Antepartum Wernicke's Encephalopathy: Common, and Yet Rarely Diagnosed. Discussion on the Disease and Its Treatment

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ABSTRACT
This review article presents a comprehensive discussion on antepartum Wernicke's encephalopathy (WE), a serious neurological disorder. This disorder stems from thiamine (Vitamin B1) deficiency, which is critical for normal metabolism and neuronal integrity. During pregnancy, women are more susceptible to this condition due to increased nutritional requirement and metabolic changes.
In WE, inadequate thiamine (Vitamin B1) causes disruption of metabolism in cells and impedes neurotransmitter synthesis in the brain, ultimately causing adverse neural consequences. Key risk factors contributing to antepartum WE include conditions that hinder thiamine absorption or increase metabolic demand, such as hyperemesis gravidarum (intense antepartum vomiting), malnutrition, alcoholism, and post-bariatric surgery states. WE's classic triad of symptoms, confusion, ataxia (loss of balance and coordination), and ophthalmoplegia (occlumotor incoordination), are not commonly seen in antepartum WE. Therefore, diagnosing the disorder in pregnancy is challenging and the condition is often misdiagnosed. Pregnancy symptoms like nausea, vomiting, and fatigue often overlap with WE's presentation, complicating diagnosis and confounding treatment. While magnetic resonance imaging (MRI) can reveal characteristic lesions in brain areas such as the thalamus and mammillary bodies, these may not always appear in early stages, adding further diagnostic difficulty.
Effective management of antepartum WE relies on early recognition and timely administration of high-dose thiamine, particularly parenteral administration for affected pregnant women. Prompt treatment is critical to preventing irreversible sequalae, neurological and otherwise in both the woman and the child. Once acute symptoms are managed, transitioning to oral thiamine supplementation is the norm to prevent recurrence and maintain normal thiamine levels. Balanced diet of macro-nutrients and maintaining fluid and electrolyte balance, also plays an essential role in recovery. In severe or treatment-resistant cases, more intensive, prolonged thiamine therapy and regular monitoring of maternal and fetal health are necessary, usually managed by a multidisciplinary medical team. This coordinated care approach aims to prevent recurrence and minimize risks associated with WE.
The article emphasizes following clinical guidelines, which recommend regular thiamine monitoring and preventive measures in high-risk pregnancies, to improve maternal and fetal outcomes. By adhering to established protocols, healthcare providers can reduce the likelihood of severe complications associated with WE, ensuring better care and recovery for affected pregnant women.
Categories: Pregnancy, Neurology, Nutrition.

1. Introduction

Antepartum Wernicke's encephalopathy (WE) often has an unique presentation (compared to the classical counterpart) and is usually a sequalae to pregnancy related hyperemesis gravidarum. The condition is the neurological manifestation of thiamine deficiency in pregnancy. Thiamine or Vitamin B1 is a molecule that plays an intricate role in Kreb's cycle and neurotransmitter synthesis. Without these functions, biochemical processes are disrupted, leading to neurological manifestations which characterize Wernicke's encephalopathy. [1]

WE primarily affects individuals with predisposing malnutrition. First identified by Carl Wernicke in 1881, WE is traditionally associated with chronic alcoholism but can arise in any condition leading to malnutrition or impaired thiamine absorption. Pregnant women are especially vulnerable as their thiamine requirements increase to support fetal development and adapt to accompanying metabolic changes. [2]

In pregnancy, hyperemesis gravidarum—a condition causing prolonged vomiting—can trigger WE by preventing adequate gastro-intestinal thiamine absorption. Other risk factors include bariatric surgery, dietary limitations, and conditions that elevate metabolic needs or hinder nutrient absorption (like Pernicious anemia). As pregnancy advances, the growing demand for thiamine progressively increases the risk of deficiency and thereby the resultant serious neurological consequences. [3]

Despite its established causes, antepartum WE is frequently underdiagnosed because its symptoms can vary widely from the classical presentation. In pregnant women, WE symptoms such as confusion, ataxia, and nystagmus may be subtle or masked by other pregnancy-related symptoms, delaying diagnosis and treatment. [4] Neuroimaging, especially MRI, can reveal distinctive brain lesions; however, these usually do not appear early in the disease, complicating the diagnostic process. Timely intervention with high-dose thiamine is crucial to prevent lasting neurological damage to maternal and fetal nervous systems. [3,4]

This review aims to raise healthcare providers' awareness of about WE in pregnant women and to emphasize the importance of timely diagnosis and treatment. WE has severe potential consequences, however these complications are preventable. This article emphasizes current understanding of WE's pathophysiology, risk factors, symptoms, diagnostic challenges, neuroimaging findings, and treatment strategies. By providing a thorough compendium on antepartum WE, this review aims to improve early diagnosis, effective intervention, and ultimately, health outcomes for both mothers and fetuses.

2. Pathophysiology and Risk Factors

The mechanisms underlying Wernicke's encephalopathy (WE) involve the disruption of vital biochemical processes due to thiamine deficiency, leading to neuronal damage and brain lesions. Thiamine is necessary for enzymes that support energy metabolism, and its deficiency can result in cell death and the formation of lesions in critical brain regions, including the mammillary bodies, thalamus, and brainstem. [5]

As a coenzyme, thiamine activates enzymes like pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and transketolase, all essential to the Krebs cycle and pentose phosphate pathway. Without adequate thiamine, these enzymes cannot function properly, resulting in reduced ATP production, increased oxidative stress, and ultimately, neuronal injury and cell death. [6]

Several risk factors increase the likelihood of antepartum WE, including hyperemesis gravidarum (persistent vomiting and associated malnutrition), chronic alcoholism, bariatric surgery, and dietary restrictions common during pregnancy. [7] Hyperemesis gravidarum, characterized by prolonged vomiting, can significantly deplete thiamine levels, while alcoholism disrupts both thiamine absorption and storage. Bariatric surgery may alter digestive anatomy, further impairing nutrient absorption. Additionally, dietary limitations during pregnancy, whether from nausea, food aversions, or cultural practices, can lead to inadequate thiamine intake, increasing the risk of WE. [8]

Thiamine deficiency can be compounded by other nutritional deficiencies, such as B12 and folate, which may worsen neurological symptoms and hinder timely diagnosis. Multiple nutrient deficits often produce a complex clinical picture, making WE diagnosis and treatment more challenging. Furthermore, conditions like hyperemesis gravidarum and bariatric surgery contribute to deficiencies beyond thiamine, worsening the patient's health status. [9]

Genetic predispositions and pre-existing health issues may also influence vulnerability to WE. Genetic variations affecting thiamine transport and metabolism can impact an individual's thiamine needs and deficiency risk. Chronic health conditions like gastrointestinal disorders that impair nutrient absorption can also heighten susceptibility. Recognizing these genetic and health-related factors is crucial for identifying at-risk individuals and implementing preventive strategies. [10]

This multi-layered analysis of WE's pathophysiology and risk factors illustrates the complexity of the disorder and underscores the importance of thorough clinical assessment and targeted interventions. A brief flow chart of the pathophysiology is presented in Figure 1.

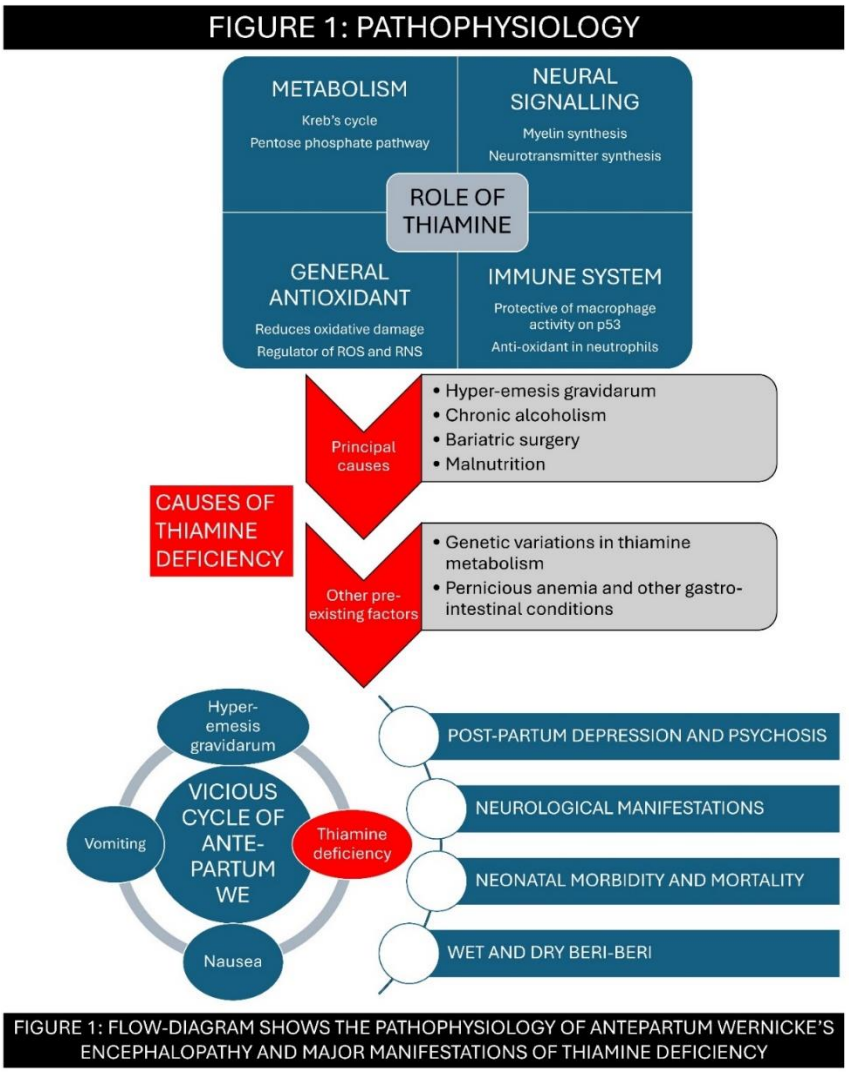

FIGURE 1: FLOW-DIAGRAM SHOWS THE PATHOPHYSIOLOGY OF ANTEPARTUM WERNICKE'S ENCEPHALOPATHY AND MAJOR MANIFESTATIONS OF THIAMINE DEFICIENCY

3. Clinical Presentation – And Overlap with Chronic Thiamine Insufficiency

Wernicke's encephalopathy (WE) typically presents with a classic symptom triad: ophthalmoplegia (eye movement issues), ataxia (loss of coordination), and confusion or altered mental state. However, in pregnant women, WE presentation may be atypical or partial, complicating diagnosis. The following describes WE's diverse clinical manifestations, including less common symptoms traditionally attributed to chronic thiamine insufficiency.[11]

- **Ophthalmoplegia**: Characterized by paralysis or weakness in eye muscles, this can present as rapid, involuntary eye movements (nystagmus), double vision, or drooping eyelids (ptosis). In pregnancy, these may be subtle or resemble other pregnancy-related concerns, delaying diagnosis. [12]
- **Ataxia**: Defined as loss of balance and coordination, this makes walking or performing fine motor tasks difficult. In pregnant women, ataxia may be misattributed to general weakness or other neurological conditions, further obscuring the cause. [13]
- **Confusion or Altered Mental State**: Ranging from mild confusion and memory issues to severe disorientation and psychosis, cognitive symptoms can overlap with mood changes and cognitive shifts common in pregnancy, thus complicating diagnosis of WE. [14]

Overlapping manifestations with chronic thiamine insufficiency (wet and dry beri-beri) include:

- **Peripheral Neuropathy (Dry Beri-beri)**: WE may also cause numbness, tingling, or neuralgic pain in the limbs. Though not a classic symptom, peripheral neuropathy is an important consideration in comprehensive assessment, especially for pregnant patients. [15]

- **Cardiovascular Issues (Wet Beri-beri)**: Symptoms may include rapid heartbeat, low blood pressure, and heart failure. These can mimic pregnancy-related cardiovascular complications, and is very difficult to differentiate. [16]

The various clinical manifestations of WE are depicted in Figure 2. Sequalae in children of mothers with WE are shown in Figure 3. [Adapted from 15]

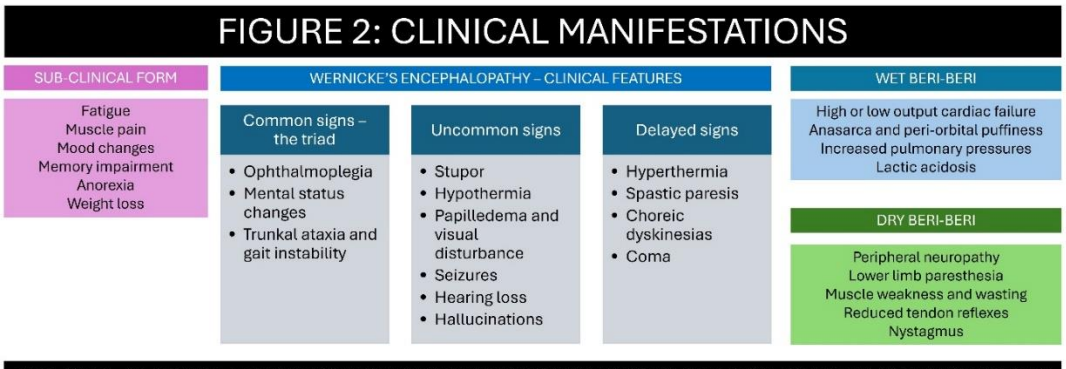

FIGURE 2: CLINICAL MANIFESTATIONS OF WERNICKE'S ENCEPHALOPATHY WITH MANIFESTATIONS OF PRECEEDING SUB-CLINICAL FORM ON LEFT AND COMPLICATIONS (TWO FORMS OF BERI-BERI) ON THE RIGHT (Adapted from Kareem et al)

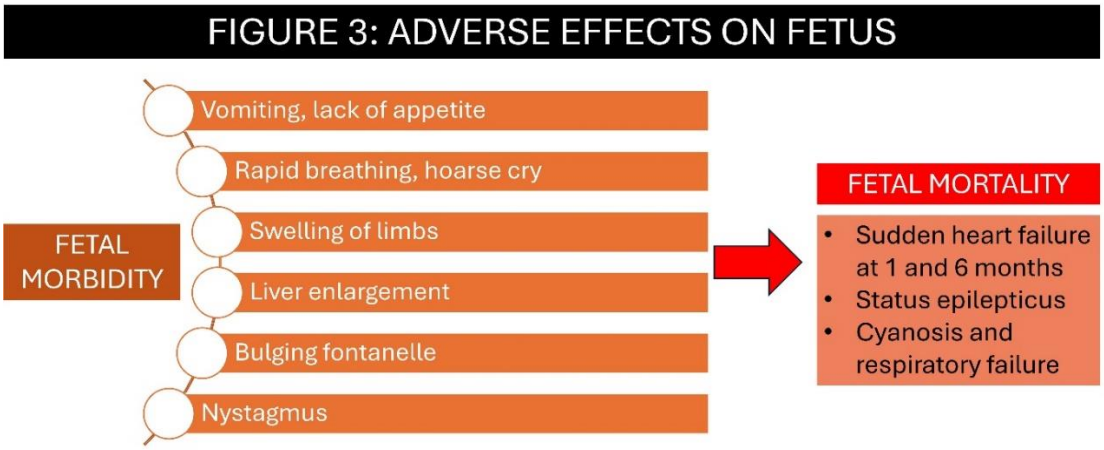

FIGURE 3: ADVERSE EFFECTS ON FETUS – MORBIDITY ON THE LEFT AND CAUSES OF FETAL MORTALITY ON THE RIGHT (Adapted from Kareem et al)

4. Diagnostic Challenges

- **Atypical Presentation in Pregnancy**: Pregnant patients may present with an incomplete or atypical form of WE, making diagnosis difficult. Common pregnancy symptoms like nausea, vomiting, and fatigue may overlap with or mask WE, leading to potential delays in diagnosis. [17, 18]
- **High Index of Clinical Suspicion**: A high index of clinical suspicion is essential, particularly for patients with risk factors such as hyperemesis gravidarum, which can cause prolonged vomiting and malnutrition. Early identification of these risk factors is crucial for specific investigations and treatment. [18]
- **Limitations of Clinical Diagnosis**: On account of overlapping symptomatology, diagnosing WE based solely on clinical presentation is not practical. Additional diagnostic tools are often required for confirmation. [3]

5. Diagnostic Investigations Including Imaging

- **Serum Thiamine Levels**: Serum thiamine measurement can support a WE diagnosis, though normal levels do not rule it out since they may not accurately reflect in acute thiamine deficiency. Low levels, especially in symptomatic patients, are strongly suggestive of underlying WE. [19]
- **Neuroimaging**: MRI is the investigative modality of choice for neuroimaging in WE, pregnancy induced or

otherwise. MRI findings when present are fairly definitive of WE. Typical findings of symmetrical T2/FLAIR (fluid sensitive sequences) hyperintensity in the dorso-medial thalamus, mammillary bodies, and periaqueductal area. Other areas that may be involved are the third ventricle and the cerebral cortex. Rarely the cerebellum and medulla may be affected. Commonly, these areas may show restricted diffusion and enhancement (in particular, enhancement of the mamillary bodies). On MR spectroscopy a normal or decreased NAA and a lactate peak is characteristic finding, but rare. (Figure 4) [20, 21, 22]

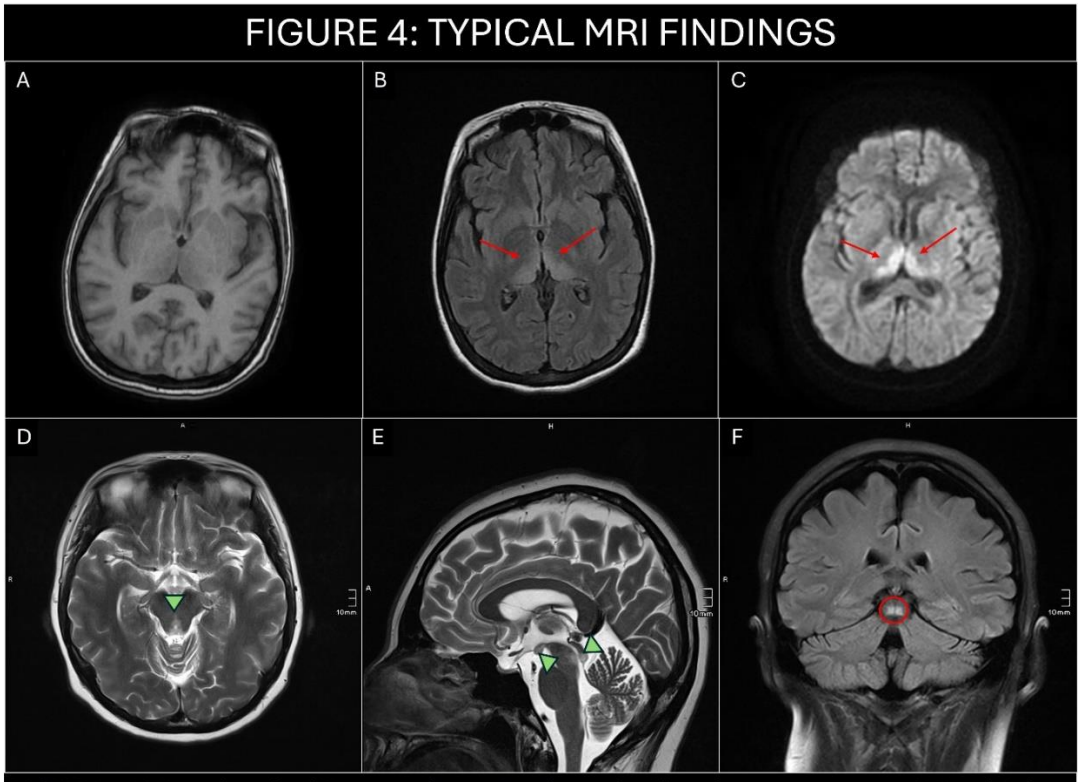

FIGURE 4: MRI sections in different patients showing typical imaging appearances of Wernicke's encephalopathy. The first row shows normal T1 (A), FLAIR high signal intensity in bilateral dorso-medial thalami (B, red arrows) and restriction on DWI (C, red arrows). MRI images in a second patient has been shown in the 2nd row. Peri-aqueductal grey matter T2 hyperintensity shown in axial T2 (D, green arrow head), mid-sagittal T2 (E, green arrow heads) and coronal FLAIR (F, red circle). Although imaging findings are fairly characteristic in a given clinical background, normal appearances are seen very commonly in antepartum WE. (Image source: Radiopedia and Google images)

However, absence of lesions is not uncommon, and **a normal MRI cannot exclude WE**. Computed Tomography (CT) scans due to poorer soft tissue resolution are often non-diagnostic and typically normal. CT is thus, not the preferred modality due to very limited diagnostic accuracy and exposure of ionizing radiation (even with modern shielding techniques). [20]

- **Challenges in Interpretation**: Even diagnostic investigations can be difficult to interpret in a setting of pregnancy and absence of any prior alcohol use/abuse. MRI findings might be subtle or delayed, and thiamine levels may not fully reflect deficiency due to test limitations or coexisting illnesses. Many confounding differentials are present in imaging, namely more common bilateral medial thalami involvement in artery of Percheron infarct and great cerebral vein thrombosis, metronidazole induced encephalopathy (involves the cranial nerve nuclei and splenium) and rarely Leigh's disease (mamillary bodies are spared). [21, 22, 23]

Since early recognition and diagnosis is essential to prevent neurological consequences and negative pregnancy outcomes, maintaining high clinical suspicion and having comprehensive approach is instrumental for diagnosis. As in every complex diagnosis, combining clinical evaluation with diagnostic investigations remains the most effective strategy for countermanding the unique diagnostic challenges posed by pregnancy induced WE. [24]

6. Management During Pregnancy

Management of Acute Presentation

Wernicke's encephalopathy (WE) necessitates immediate treatment with thiamine supplementation to prevent irreversible neurological damage. Upon suspicion of WE, especially in pregnant women experiencing hyperemesis gravidarum or with other risk factors, high-dose intravenous thiamine should be administered immediately. The recommended initial dose is typically 500 mg of thiamine hydrochloride, given intravenously three times daily for 2–3 days, aiming to restore thiamine levels rapidly and prevent further neurological deterioration. [25]

Continuing Thiamine Supplementation and Supportive Care

After the acute phase, thiamine supplementation should continue throughout pregnancy and postpartum to prevent recurrence. Once the patient shows improvement, oral thiamine may be started, generally at a daily dose of 100–250 mg. Alongside thiamine, comprehensive nutritional support is essential, including rehydration with oral electrolytes to address any imbalances caused by prolonged vomiting or malnutrition. A balanced diet consisting essential nutrients supports recovery for both the mother and fetus. Regular monitoring of thiamine levels and overall nutritional status is vital to adjust needed nutrients and supplements as needed. [26]

Managing Severe or Refractory Cases and Ensuring Monitoring

For severe cases or those unresponsive to initial treatment, more intensive care may be required, possibly involving prolonged intravenous thiamine administration or higher doses tailored to the patient's needs. Monitoring should include neurological evaluations, nutritional assessments, and investigations for fetal well-being. In complex cases, a multidisciplinary team of neurologists, obstetricians, and nutritionists are usually involved to provide comprehensive care. For severe cases, additional imaging or adjustments to supportive care might be needed to manage concurrent issues effectively. [25]

The overall objective of these management strategies is to ensure prompt and sufficient thiamine repletion, address nutritional deficiencies, and closely monitor maternal and fetal health, ultimately mitigating further deterioration of WE.

7. Treatment Guidelines and Recent Evidence Based Medicine

Pharmacological Repletion and Regimens

Thiamine repletion is central to the treatment of Wernicke's encephalopathy (WE). Guidelines recommend initiating high-dose intravenous thiamine in the acute phase to quickly restore thiamine levels and halt neurological damage. The standard protocol involves administering 500 mg of thiamine hydrochloride intravenously three times daily for the first 2–3 days. After stabilizing the patient, treatment typically transitions to a lower, oral maintenance dose to sustain thiamine levels and prevent recurrence. [25, 27]

Comparison of Thiamine Delivery Methods

The efficacy and safety of different thiamine administration methods, including oral, intravenous, and intramuscular routes, have been critically examined to help clinicians choose the best administration route for every scenario. Acute presentations are generally treated with parenteral administration of high dose thiamine, with subsequent oral maintenance. Chronic cases of thiamine deficiency are more often adequately treated with only oral administration. In all cases, an IV or IM dosing regimen is effective in the control of immediate symptoms. [15]

Recommendations for WE Prevention and Treatment

The major health organizations' guidelines emphasize regular thiamine supplementation for high-risk groups, such as pregnant women with hyperemesis gravidarum or those with a history of chronic alcoholism. Proactive identification of at-risk patients and applying preventive measures in accordance with these guidelines helps lower WE risk during pregnancy. [28, 29] However, potential side effects and contraindications of thiamine therapy needs consideration. Most authors concur on the relative safety of both oral and parenteral administration routes, since thiamine is a water soluble vitamin and easily excreted by kidneys. Although extremely high dose (7 to 7.5 g/day) intra-venous and intra-muscular injections are reported to cause convulsions, arrythmias and anaphylactic shock, these are exceedingly rare. Commoner side effects of oral preparations include nausea and

indigestion when used for prolonged periods of time, although, these too are infrequent. Rarely, milder allergic reactions have been reported with both oral and parenteral routes. [30]

Future Directions and Research

Current guidelines offer valuable insights for treatment, but ongoing research is exploring new therapeutic strategies and aiming at improvement of existing protocols. Studies are currently underway to examine alternative thiamine formulations, additive therapies to boost thiamine absorption, and identify biomarkers for early detection and monitoring of WE. These emerging novel management strategies may improve the detection and treatment of Wernicke's encephalopathy in pregnancy. [29]

8. Summary and Conclusion

There is no doubt that early diagnosis and prompt treatment prevents serious complications of Wernicke's encephalopathy. The first half of the article aims to provide readers with a thorough understanding of antepartum WE and the necessary steps for its effective management and prevention. We stress the importance of increasing awareness among healthcare providers regarding the risk factors and clinical presentations of WE in pregnant women. Additionally, the review provides a platform for performing future research, including the creation of improved diagnostic tools and preventive strategies in high-risk groups.

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