

Hyperemesis Gravidarum, Werneck's encephalopathy and Korsakoff syndrome: a critical appraisal of the relevant literature.

Running title: Hyperemesis Gravidarum

Abstract:

Background:Hyperemesis gravidarum tends to rapidly progress into Wernicke's encephalopathy and Korsakoff syndrome and, therefore,needs to be recognized early and managed promptly with targeted multimodal therapies.**Objective:** This study critically reviewed the relevant literature on clinical perspectives of hyperemesis gravidarum, Wernicke's encephalopathy and Korsakoff syndrome.The secondary objective of this study wastoimprove the awareness, emphasis on early diagnosis and immediate intervention concerning these sequential syndromes in pregnant women across the board.**Methods:** Electronic searches (since inception-2019) of PubMed/MEDLINE, Google Scholar, OvidSP, Dove Medical Press, Sciencedomian International and Hindawi.com were conducted using keywords and Boolean Operators. Hundreds of thousands articles were retrieved which were reviewed independently by two authors and finally 144 articles retained that addressed clinical components of these sequential syndromesalong with relevance of thiamine deficiency.**Results:** Evidently, vulnerable women in early stage of gestation tend to develop persistent severe pernicious nausea and vomiting followed byvariable oculomotordisturbances, ataxia, confusion and gross memory impairment and need diagnostic evaluation by means of clinical history, relevant laboratory tests, abdominal ultrasound and brain computerized tomography andbrain magnetic resonance imaging.Most patients need emergency admission, prompt treatment with optimal doses of antiemetics, thiamine B1, and followed by

fluid replenishment and electrolyte balance with followup till the end of pregnancy. Successful maternal and fetal outcome of pregnancy depends on multiple determinants including associated systemic diseases. **Conclusion:** Evidently, a variety of etiological and risk factors in pregnant women determine the initiation of hyperemesis gravidarum, Wernicke's encephalopathy and Korsakoff syndrome, and each of which needs prompt diagnosis and early multimodal treatment in order to reduce maternal morbidity and increase successful outcome of pregnancy. Although clinical literature concerning these sequential syndromes is huge, further studies are needed to understand their underlying pathophysiological pathways across the world.

Keywords; Hyperemesis gravidarum, Wernicke's encephalopathy and Korsakoff syndrome, thiamine deficiency,

INTRODUCTION

Pregnancy is a normal physiological process and ends by ninth month with a healthy baby. However, pregnancy may associate with morning sickness, nausea and vomiting of pregnancy (NVP), hyperemesis gravidarum (HG), Wernicke's encephalopathy (WE) and Wernicke-Korsakoff syndrome (WKS) [1]. HG is an emergency condition characterized by severe, intractable nausea and vomiting affecting 0.3-3 % of all pregnancies [1-3]. Conversely, NVP are common happenings presenting in 50% to 90% of all gravida [4,5]. Both recurrent conditions lie on the opposite poles of a spectrum but need suitable interventions. The onset of NVP starts at 4-8 weeks and subsides in 90 % cases by 16-20 weeks; however, NVP may persist beyond 20 weeks in 13% of cases [2-7]. Evidently, HG more severe than NVP is typically characterized by pernicious nausea and vomiting (3 times/day) that results in dehydration, electrolyte and fluid imbalance, weight loss ($\geq 5\%$), ketonuria, physical and psychological debilitation and very often necessitates hospital admission [2,6]. In the past, hundreds of case reports, many studies and reviews had described HG co-occurring with and complicated by diverse systemic diseases, infections and medications [8-39] (Table 1). A recent systematic review of HG revealed 146 case studies that reported on 177 cases of HG and WE, linked with worsening fetal and maternal outcome [31,40-43]. In specific terms, HG primarily induced by thiamine deficiency is associated with fetal low birth weight, intrauterine growth restriction, preterm delivery, neurodevelopmental

anomalies and poor maternal health which adversely impact their future life trajectories [44-48]. In addition, thiamine deficiency in infant-mother domain is a neglected problem worldwide with possible linkage to sudden infant death syndrome [49]. Interestingly, thiamine deficiency may also cause aforesaid fetal problems in pregnant women even without HG [50]. Some reports suggested that the perinatal outcome of pregnant women who suffered from HG remain unaffected [51]. HG often results in an acute thiamine deficiency which is characterized by loss of appetite, nausea and vomiting, fatigue, weakness, anxiety, difficulty in concentration, confusion, disorientation, and memory loss and, if not treated, progresses to WE, KS and Wernicke-Korsakoff syndrome (WKS). Overall, only a small proportion of pregnant women with or without prior thiamine deficiency tend to develop HG, which is linked with potential complications including but not limited to only WE, KS and WKS requiring emergency admission and immediate interventions with regular follow-up till the end of pregnancy.

2. AIMS

This study aimed to review the specific literature on various clinical aspects of HG, WE and KS in women with pregnancies. Another secondary objective was to improve the awareness, emphasis on early diagnosis and immediate multimodal interventions concerning aforesaid sequential syndromes in pregnant women. The significance of this study is to fill the knowledge gap of healthcare providers and users especially in Arabian Gulf countries where the published literature on these sequential syndromes is limited and scanty.

3. METHODS

3.1 Search

Electronic searches (from inception to 2019) of four databases and three open access publishing houses (Google Scholar, PubMed, ScienceDirect, and OvidSP and Medical Dovepress.com, Hindawi.com & Sciencedomain.org) and local literature were conducted using Boolean operators and keywords such as Hyperemesis gravidarum AND thiamine deficiency OR severe nausea AND vomiting OR Wernicke's encephalopathy OR Korsakoff syndrome OR central pontine myelinolysis AND interventions OR prevention strategies OR adverse effects OR Case reports OR case series OR observational studies OR randomized clinical trials (RCTs) OR systematic

reviews OR meta-analysis for retrieving pertinent articles published in English literature. The searches were modified whenever needed and compatible with databases and publishing houses.

3.2 Search Results

A large number of articles more than twenty one thousand were retrieved. A quick screening by a single author excluded more than sixteen thousand articles that did not focus on HG, thiamine deficiency, WE, KS and WKS and their treatment perspectives. Then, two authors independently reviewed the available data for extracting the most relevant articles. Subsequently, unrelated articles, inaccessible papers because of high price tag, articles cited in systematic reviews and meta-analysis, no abstract available, duplications, and irrelevant information were excluded from this study. The remaining articles were screened further for eligibility and those articles which did not focus on HG, WE, KS and WKS) and their etiologies, risk factors, comorbidities, complications and treatment interventions were excluded. Thus, the total articles included in this narrative review 144 (Figure.1).

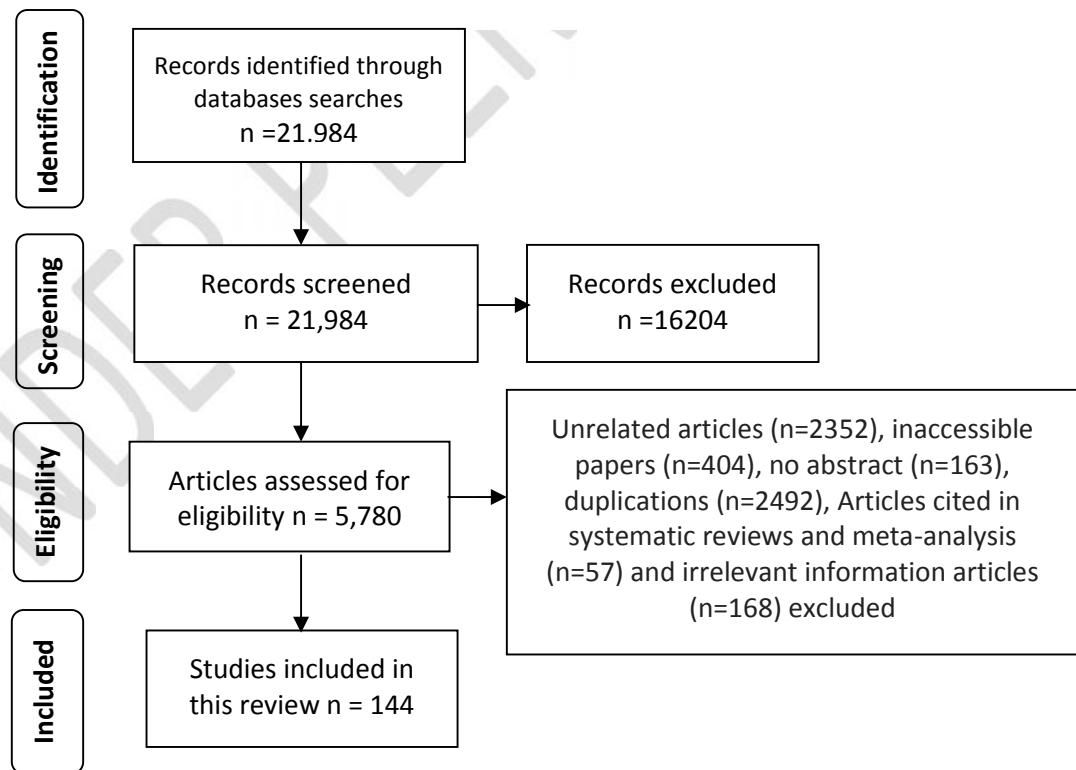


Figure 1 Prisma diagram summarizing the flow of search results

4. RESULTS

Thiamine B₁

Thiamine is an essential micronutrient obtained from food or dietary, mineral and vitamin supplements, and its adequate daily supply is associated with good pregnancy outcome [52]. Thiamine deficiency is a nutritional disorder and is determined by multiple factors including medications such as diuretics [53]. Besides maternal characteristics, thiamine deficiency is the core problem in HG and poor outcome of pregnancies and conversely its infusion rarely causes anaphylactic shock and cardiac arrest [45,53,54]. Thiamine a water soluble vitamin is absorbed from the duodenum and 25-30 mg of thiamine is stored in the body system [55,56]. The recommended daily dose is 0.4 mg. However, in pregnancy the requirement of thiamine increases up to 1.5 mg/day because of developing fetus and hypermetabolic state of pregnancy. This amounts to about 36% above the non-pregnant level [55-57]. The body has approximately 3-week thiamine stores regardless of body mass index (BMI). Furthermore, thiamine requirement is mostly contingent on metabolic rate and, hence, largely increases during high glucose intake including glucose-containing intravenous fluids. In pregnancy specifically, thiamine stores are rapidly depleted due to excessive vomiting, poor intake of food, and greater metabolic demand [56-59]. Therefore, thiamine deficiency is highly prevalent during pregnancy worldwide especially low and middle-income countries. Simply the body redirects maternal thiamine to the fetus during later third trimester of pregnancy. This results in exacerbation of maternal thiamine deficiency that increases the risk of HG, fetal loss and preeclampsia [58,60-62]. Women with HG require even more thiamine due to their high carbohydrate diet, coexisting electrolyte deficiencies (magnesium, potassium and sodium), limited food varieties, chronic starvation and malnutrition, impaired absorption, and reduced muscle mass for storage [52,56,58,63,64]. In sum, thiamine is mainly found in food and its daily requirement increases in pregnancy attributed to a variety of maternal and fetal factors together with inadequate supply of food varieties across all communities and, hence, thiamine deficiency during pregnancies with HG and altered sensorium gestosis and other related potential adverse effects vary across the world [48,58,64,].

Thiamine and Central Nervous System (CNS)

Thiamine subserves various biochemical functions in the body and its inadequate supply is reported to perturb the functions of various organs including brain and gut [65]. Normally, thiamine is converted into thiamine pyrophosphate in neuronal and glial cells that serves as an active cofactor for transketolase, pyruvate dehydrogenase, and alpha ketoglutarate enzymes (pentose phosphate pathway), and these important enzymes are involved in carbohydrate and lipid metabolism, and production both of amino acids and glucose-derived neurotransmitters [65-70]. In addition, thiamine has an important role in axonal conduction concerning acetylcholinergic (acetylcholine) and serotonergic (serotonin) neurons/receptors. Evidently, various subtypes of 5-hydroxytryptamine (5-HT, serotonin) receptors are reported to correlate with emesis arising from multiple diseases including HG and radiation therapy or chemotherapies [70]. Thus, thiamine deficiency over a period of 2-3 weeks leads to dysfunctions of aforesaid enzymes specifically of α -ketoglutarate-dehydrogenase in mitochondrial network. Consequently, oxidative cascade results in diffuse impairment in glucose-energy metabolism and necrotic and apoptotic insult to the specific brain regions with the highest metabolic activity including ocular changes such as intra- and extra-cellular edema, glial cell proliferation, neuronal demyelination, and cellular degeneration [69,71]. Chronic alcohol consumption is also associated with reduced transketolase activity by 35% in the cerebellum attributed to thiamine deficiency [72]. Interestingly, thiamine level in the brain is inversely related to the duration of alcohol use. Additional neurobiochemical findings concerning acute thiamine deficiency include increased cytokines, lactate and edema, extracellular glutamate concentrations, nitric oxide from endothelial cell dysfunction, and deoxyribonucleic acid (DNA) fragmentation in neurons, free radical production and breakdown of the blood-brain barrier [67-72]. The related neurological implications of thiamine deficiency are diverse but not limited to WE, KS, WKS, dementia/amnestic syndrome but central pontine myelinolysis (CPM), akinetic mutism and akinetic-rigid syndrome are due to the correction of thymine-induced sodium deficiency [34,73-75]. Most of neurological effects of thiamine deficiency are reversible by thiamine repletion. For example, ocular motor signs concern the reversible lesions in the brainstem affecting the abducens nuclei and eye movement centers in the pons and midbrain [71,75,76]. This is evidenced by the fact that the rapid improvement and nearly complete recovery tend to occur following thiamine intake [75]. Furthermore, ataxia and stance are caused by damage to the superior vermis in the cerebellum, and the degeneration of the Purkinje cells [76,77]. The effects

of thiamine deficiency does not stop here because the vestibular apparatus, diencephalon network linked with medial temporal lobes and amygdala are also affected causing impairment of hearing and persistent amnesic syndrome or WKS; the latter is attributed to irreversible damage [68,75]. In sum, thiamine deficiency attributed mainly to HG and chronic alcoholism impact adversely several molecular processes in the CNS that lead to WE, extra-CPM and CPM, KS and Wernicke-Korsakoff Syndrome (WKS).

Diagnosis and Treatment of Thiamine Deficiency

It is wise to diagnose any health condition prior to starting treatment intervention. Laboratory tests for assessing thiamine deficiency are not straightforward and confirmatory because related tests reflect only 0.8%-10% of the body's thiamine stores and thiamine intake [78]. Nonetheless, all women need laboratory workup concerning vitamin profile because at times well nourished patients are reported to show deficits of thiamine and vitamin C [79]. Furthermore, thiamine testing is not always available at all settings and even its reliability is equivocal [78]. About 50% of patients with WE have normal thiamine levels, which means an array of other factors causes WE, KS and WKS. Evidently, the end result of multiple factors underpinning thiamine deficiency should be managed proactively by thiamine repletion. In addition, the management of other risk factors underlying thiamine deficiency must be considered earnestly or else health providers do disservice to the patients with HG, WE and KS [51,54,78]. Without any overemphasis, the treatment of thiamine deficiency in pregnancy needs to be early, adequate and longterm till the end of pregnancy. Parenteral thiamine is non-toxic and rarely causes anaphylaxis, and, hence, its proactive administration is safe during pregnancy. Thiamine doses, 50mg to 200mg a day should be given parenterally for two weeks followed by oral dose of 60 mg/day till the delivery [30,55,56,67,68]. In addition, magnesium sulfate 1 to 2 ml of 50% solution intravenously is also recommended as magnesium is a cofactor in many enzymatic processes in the body [52,64]. The prognosis is variable and for the acute episode, more than 50% patients show substantial improvement and less than 25% remain impaired [30,55,67,68]. In sum, thiamine deficiency in pregnant population affecting several body functions needs early diagnosis and prompt treatment for the safety both of the fetus and mother.

Hyperemesis gravidarum (HG)

HG is a medical emergency characterized by severe persistent nausea and vomiting, electrolyte imbalance, dehydration, weakness, nutritional deficiencies and metabolic disturbances in the first trimester and caused by hormonal changes associated with gestation and acute or chronic thiamine deficits. HG might be predicted by several biological factors which are pre-pregnancy body mass index (BMI), adipose tissue, maternal age, leptin, neptatin-1, ghrelin, beta-chorionic gonadotropin (β -hCG), estrogen, progesterone, total (T4) and free thyroxine (fT4), placental growth hormone, prolactin, and adrenocortical hormones which are considered as predictive markers [80]. A recent study reported the possible role of two genes-growth differentiating factor 15 (GDF 15) and insulin-like growth factor-binding protein 7 (IGFBP7) in HG [81]. The pathophysiology of HG is poorly defined but panoply of risk factors and etiologies are proposed, and, therefore, this avenue needs further research.

Prevention of HG

Converging evidence suggests that prevention is cost-effective and better than cure. Prior to any intervention, all women need laboratory workup concerning vitamin profile [79]. Evidently, thiamine B₁ infusion tends to seldom cause anaphylactic shock and cardiac arrest in patients with allergy [53] and, hence, physicians should make sure that patients with HG do not have a history of thiamine hypersensitivity. All women at risk for recurrent HG including those with a personal or family history of HG and vitamin and mineral deficits, and planning for pregnancy should be prescribed multivitamins and minerals for correcting related deficiencies [52,64,81-86]. This proactive approach needs to be used at community level in order to cover as many as women liable to develop HG and its adverse consequences [47]. Postconceptionally, parenteral vitamins with a minimum of 5 mg of thiamine B₁ and fluids with electrolytes should be given to all pregnant women with nausea, vomiting, multiple pregnancy, and neurological and cardiac symptoms for preventing HG and other complications [33,73,82,87-90]. Notably, vitamins and electrolyte free parenteral fluids interfere with the prevention of nausea and vomiting in pregnant women by causing thiamine deficiency and electrolytes imbalance leading to WE, KS, WKS and CPM [78,90]. Notably, pregnancy is a condition which is metabolically very demanding and additional upbeat thiamine supply tends to maintain its normal status. HG also causes economic burden and adverse psychosocial impact including depression, post-traumatic stress disorder (PTSD) and anxiety in 80% pregnant women who certainly need psychosocial interventions [91]. In sum, HG is an acute medical emergency induced by diverse risk factors including

psychological and, hence, requires prompt prevention and management measures for reducing its various complications, psychosocial burden, economic costs and deaths concerning pregnant women with HG [21,42,92,93].

Treatment of HG

The pregnant women with HG need urgent admission (“holding function” effect) and prompt treatment. Evidently, up to 90% of pregnant women develop short duration of mild nausea and vomiting in pregnancy (NVP) or emesis gravidarum in the first trimester. NVP occurs more commonly in young age, uneducated, obese, non-smokers, past h/o nausea and vomiting, and first pregnancy. A selective literature review reported symptom-based (flank pain, neurological symptoms, diarrhea, and abdominal pain) 34 differential diagnoses including diabetic ketoacidosis of NVP [38]. The symptoms of NVP when severe, prolonged and associated with thiamine deficiency, electrolyte changes, starvation, fluid imbalance, tiredness and weakness suggest intractable HG [94]. The management of grade I (without metabolic changes) and II (with metabolic changes) HG requires multi-model approach; antiemetics, antihistamines and anticholinergic (dimenhydramine 25-50 mg every 6-8 h; meclizine 25-100 mg 2-4× per day orally/1×per day rectally; dimenhydrinate; 50 mg 3-4×per day orally/62 mg 2×per day IV/1-3× per day rectal route; promethazine; 12.5–25 mg 6–8 hourly Orally, IM or IV), phenothiazines (Prochlorperazine 25 mg per day or 2×per day rectally; Chlorpromazine; 5-10 mg 6 hourly orally, IM or IV; 25 mg per rectally; metoclopramide, 5-10 mg 8 hourly orally, IV or IM(maximum 5 days’ duration), steroids (hydrocortisone 100 mg twice daily, then 50mg/day and then tappers lowly), benzodiazepines (diazepam 40-160mg/IV, or midazolam 1 to 2mg IV slowly over 10 minutes), and 5HT₃antagonists (Ondansetron: 4-8 mg 6-8 hourly PO; 8 mg over 15 minutes 12 hourly IV.), thiamine (50 to 200 mg/day parenteral), pyridoxine (Vit.6, 10-25mg tid and maximum dose 200mg/day), doxylamine (oral 25 mg at night and 12.5 mg in the morning along with 10mg to 80mg pyridoxine), enteral and parenteral fluids(3L/day) and carbohydrate and amino acid (about 8400 to 10,500 kJ/d) with complete withdrawal of oral feeding [38,95]. All aforesaid medication are associated with a variety of mild to serious adverse effects including dizziness, seizures, heart rate changes and fetal maldevelopment. Rehydration among patients with HG needs careful approach because of development of refeeding syndrome with rhabdomyolysis and diabetes insipidus attributed to fatal shift in electrolytes and fluid balance in

malnourished patients receiving artificial refeeding through parenteral or enteral route [96-98]. Although multiple factors underlie refeeding syndrome, hypophosphataemia is its key determinant [99]. Physicians need to follow the standard guidelines for treating nausea and vomiting with weight loss (≥ 5 kg) among pregnant women which are available here [96,97]. In addition, replenishment of deficiencies concerning vitamin K, zinc, selenium, iron, phosphorous, sodium, magnesium and calcium benefits mother and fetus and may preempt additional complications [52,64,86,97]. The use of thiamine prior to glucose or post-glucose remains an unresolved issue, though most clinicians prefer to use first thiamine followed by fluids for the prevention of WE [100,101]. Currently, advanced digital HG Care App helps in the management of patients with HG [102]. Besides multimodal interventions, non-pharmacological integrative therapies such as psychological support, hygienic food, ginger (1gm/day), aromatherapy and medical acupuncture at acupoint P6 (Neiguan) benefit patients with HG [95,103,104]. In a nutshell, prevention and appropriate treatment of HG targeting multiple vitamin and mineral deficiencies, comorbidities and careful fluid balance along with proper nursing care preempt the development of potentially serious complications including but not limited to optic atrophy and visual loss, extra-CPM, CPM, WE, KS and WKS among pregnant women [37,90,105-108]. (Table 1).

Table 1 Co-occurring diseases and adverse consequences of HG, adapted from references

Diseases	Remarks
Pneumomediastinum and pneumothorax	Serious emergency and needs surgical intervention
Esophageal rupture or perforation	Serious emergency and needs surgical intervention
Barogenic rupture of the esophagus	Serious emergency and needs surgical intervention
Mallory-Weiss syndrome (M-WS)	Control of vomiting to decrease oesophageal pressure
Renal failure	Serious emergency needing dialysis
Liver dysfunction	Treatment will depend on severity
Transient Thyrotoxicosis	Needs intervention
Visual loss/optic neuropathy	Needs ophthalmic intervention
Hamman and Boerhaave's syndrome	Needs intervention
Thiamine deficiency	Repletion needed
Iatrogenic WE	Fluid load correction
Korsakoff syndrome and WKS	Thiamine plus care of other factors
Extrapontine and CPM	Correction of electrolytes and fluid
Akinetic mutism,	Thiamine and supportive measures
Akinetic-rigid syndrome	Thiamine and other treatment
Locked-in syndrome	Thiamine and other treatment
Chronic alcohol abuse	Needs intervention with thiamine
Infection, metabolic and endocrine perturbations	Acute thiamine deficiency needs multimodal interventions

Starvation and nutritional deficiencies	Correction of deficiencies through feeding
Electrolyte imbalance (Low K& Na)	Correction of sodium & potassium after thiamine use
Acute pancreatitis	Treatment of infection/inflammation and fluid balance
GIT infection (HP)	Needs antibiotic (erythromycin) intervention
Low mineral (phosphorous)	Needs urgent correction
Muscle weakness and tetany	Dietary supplements and electrolyte replenishment
Acidosis and alkalosis (due to malnutrition & vomiting)	Needs correction by fluids
ECG abnormalities	Intervene if needed
Fetal growth retardation and death	Monitoring and careful disposal
Psychological impact on quality of life, occupation, body image, relation with spouse, absenteeism, cost burden, job loss, depression, anxiety and PTSD	Counselling, psychotherapy, hypnotherapy, behavioral therapy including CBT and specific medications
Retinal hemorrhage	Need ophthalmic intervention
Epistaxis (due to low Vitamin K)	Needs vitamin K
Vasospasm of cerebral arteries	Needs urgent treatment of HG
Preeclampsia	Immediate intervention
Peripheral neuropathy	Vitamin supplements
Coagulopathy	Medications or replacement therapy directed toward absent clotting factors
Rhabdomyolysis and diabetic insipidus	Fluid resuscitation and prevention of end-organ complications such as kidney failure by dialysis

Wernicke's Encephalopathy (WE)

Carl Wernicke first described WE as polioencephalitis hemorrhagica superioris in 1881. Six years later, Korsakoff explained WE as polyneuritic psychosis [67,68]. Over decades, various sociodemographic risk factors of WE identified among pregnant women included middle age, housewives, low education, poor income, multigravida, multiple gestations, use of contraceptives, history of abortion and hospital admission for NVP and HG [18]. WE is a rare, serious neurological complication of HG and typically identified by a triad of ataxia, global confusion and oculomotor abnormalities including nystagmus and gaze palsies [22-29,41,50,71,77,109-114]. Patients with chronic alcoholic WE may not have all signs but any two of the following: dietary deficiencies (nausea, vomiting and thiamine deficiency), oculomotor abnormalities (nystagmus), cerebellar dysfunction (ataxia) and/or either an altered mental state (confusion) or mild memory impairment [115]. Certain patients with non-alcoholic WE may have only nystagmus and vestibulo-ocular reflex abnormalities as the initial presentation [116]. However, 10-47% of patients with WE lack one or two of these signs specifically when they have gradual or episodic onset of WE progressing to WKS and 19% of patients have none of these symptoms [73,117,118]. In such scenarios, the diagnosis of WE becomes difficult in non-alcoholic and surgical malnourished patients [33,77,87,119-121]. In the absence of universal

diagnostic criteria, WE is often misdiagnosed and also underdiagnosed when precipitated by acute severe thiamine deficiency, infection and metabolic and endocrine perturbations [25, 77,113,120,122,123]. The case of Charlotte Brontë's death illustrates the difficulties of making the diagnosis of HG/WE induced by refeeding syndrome [124]. Chronic WE occurs among pregnant patients with mild persistent thiamine deficiency and shares nonspecific symptoms such as headaches, anorexia, irritability and abdominal discomfort with HG. These shared symptoms also posit a diagnostic conundrum, HG versus WE [120,121]. However, persistent or prolonged vomiting, confusion, and unintentional weight loss are red flag signs of chronic WE [77,113,120]. Progressive course of WE is characterized by weakness, nausea, abdominal pain, dysarthria, confabulation, akinetic-mutism, aphasia, seizures and cardiac failure [34,74,77,113]. Furthermore, mental status changes are virtually universal in WE and exhibited as dizziness, drowsiness, disturbed attention with poor concentration, apathy and cognitive impairment. Gait abnormalities range from weakness to inability to stand and may be difficult to identify in HG patients with vertigo and postural hypotension [77]. The Hyperemesis Impact of Symptoms Questionnaire (HIS) and the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE-12 & 24) scoring indexes, which assess holistically nausea and vomiting in pregnant women, may further help in the diagnosis of Wernicke's encephalopathy. WE is most commonly associated with chronic alcohol abuse [72] but can be caused by other important risk factors [26,66,77,125,126] (Table 2). Overall, WE is diagnosed based on a constellation of symptoms and signs, laboratory investigations including serum and urine thiamine estimation and CT/MR imaging of the brain and exclusion of other associated diseases [25,77,113,119,127,128]. MRI findings are sensitive (53%) and specific (93%) and further support the diagnosis of WE in pregnant women [18]. The typical bilateral MRI findings of WE include hyperintense lesions in the FLAIR and T2-weighted images concerning the periaqueductal area, hypothalamic area, mammillary bodies, thalamus, the column of fornices and the upper cerebellar vermis. The involvement of cortex suggests irreversible damage and poor prognosis of WE [129]. The MRI results also help in the diagnosis of extrapontine and central pontine myelinolysis also referred to as osmotic demyelination syndromes, and associated with WE and correction of severe hyponatremia in pregnant women [130-135]. Necropsy findings may help further in the diagnosis of WE and WKS but then it is too late [117]. Overall, WE is a very complex clinical problem in pregnant women attributed to a lack of universal definition, inconsistent diagnostic

criteria, myths and misconceptions, multifactorial etiology, diverse comorbidities and complications, poorly understood pathophysiology and, hence, posits many clinical challenges to healthcare providers worldwide [51,136].

The mainstay of treatment of WE is thiamine repletion, life style changes, fluid balance by oral, parenteral and enteral routes, antiemetics, shortterm use of benzodiazepines (diazepam and midazolam) and antidepressants (mirtazapine), and addressing other underlying risk factors, etiological pathways and systemic diseases, the latter underlying conditions are acute disseminated encephalomyelitis, pituitary apoplexy, deep cerebral vein thrombosis, neuroinfection, gastroenteritis, cholecystitis, pancreatitis, hepatitis, peptic ulcer, pyelonephritis, multiple sclerosis, brain tumour, paraneoplastic disease, intoxications, Miller Fisher syndrome, autoimmune disease and the fatty liver of pregnancy [66,94,137,138,139]. The suggested thiamine doses are 500 mg per day q.i.d for 2 days, followed by 250 mg per day q.i.d. until the patient tolerates oral thiamine of which dose ranges from 60 to 100 mg daily for at least 3 months [66,109]. Most patients with WE improve rapidly with this regimen, and when there is no response, physicians should look for and manage associated diseases including GIT disorders [18,66,109] (Table 2). The prognosis of patients with WE depends on the severity, stage of the disease, hospital admission, and the prompt treatment [110]. Evidently, symptoms of WE take different timeline concerning improvement. A complete resolution of nystagmus is usually observed within 1-2 weeks of thiamine use. However, gait disturbances may persist in up to 60% of patients.[140] In case, Wernicke's encephalopathy remains unidentified and untreated may progress to Korsakoff syndrome (KS) [141]. WE can also progress to coma and even death, with a mortality rate varying from 20% to 30%, mainly due to pulmonary infection, sepsis and decompensated liver disease [110]. Complete remission of WE is reported only in 29% (54% within 3 months) of the cases and about 34% of patients show residual neurological manifestations [66,109,142]. Wernicke's encephalopathy is linked with 50% of fetal deaths attributable to spontaneous abortion, elective abortion, intrauterine death and stroke. However, early treatment with thiamine projects much better prognosis. In sum, WE is a serious complication of and shares many risk factors and etiological pathways with HG (Table 2), needs prompt recognition and treatment with thiamine repletion along with other supportive measures for better prognosis and successful outcome of pregnancy.

Table 2 Etiological and risk factors of HG (and Wernicke's encephalopathy), adapted from references

Excessive , prolonged vomiting in pregnancy including past history	Severe infection and malnutrition due to child abuse, fasting and extreme dieting and hunger strike
Current and previous molar pregnancy	Pre-existing diabetes and diabetic ketoacidosis
Eating disorders; anorexia nervosa, bulimia nervosa and binge eating	Malabsorption
Chronic kidney disease	Glucose/dextrose infusion prior to thiamine administration
Haemodialysis or peritoneal dialysis	Acute or chronic thiamine deficiency
Chemotherapy	Inadequate thiamine intake
Gestational thyrotoxicosis	Antibiotics
Prolonged parenteral feeding and TPN, prior to thiamine replenishment	Diuretics
Multiple gestation	Genetic factor; placentation, appetite, and cachexia genes GDF15 and IGFBP7 are linked to hyperemesis gravidarum (HG) and are upregulated in HG patients.
Anemia	Chronic alcohol abuse and non-smokers, smokers show low levels of estrogen and HCG.
Gastroplasty	Malignant disorders
GIT disorders, pyloric stenosis, lower esophageal sphincter disorder, cancer, infection (HP), gastrectomies, delayed gastric emptying and intestinal transit times	Acquired immunodeficiency syndrome
Iron substitution	Organ transplantation (liver)
Thyroid dysfunction (transient hyperthyroidism with ↓ level of TSH) persists only first 18 weeks of pregnancy	Hormones-estrogen (↑) and beta-HCG, IgG and IgM & prostaglandin E2, progesterone (↑ or ↓), causing gastric dysrhythmias - tachygastric, or bradygastric), ACTH, cortisol, growth hormone, 5HT and prolactin.
Unwanted pregnancy,	Psychosomatic model; Psychiatric disorders especially depression, conversion disorder; sequel of HG rather than vice-versa
Female sex of offspring,	High saturated fat diet
Immunological factors (high levels of immune globulins, C3, C4, and lymphocyte Counts)	Nulliparous woman
Obesity	H/O Migration
Drug intoxication	Food poisoning
Residence in a nursing home	Habitually restricted diet in the elderly living alone
HP=Helicobacter pylori in 95% women with intractable HG and higher IgG against HP; HCG=human chorionic gonadotrophin; ACTH=adrenocorticotrophic hormone; TSH=thyroid stimulating hormone.	

Korsakoff Syndrome (KS)

Korsakoff syndrome tends to develop among pregnant women provided co-occurring HG and WE are not managed on time. Although the initial manifestations of KS are variable, this syndrome is characterized by a disproportionate persistent impairment in memory such as anterograde and retrograde amnesia, cognitive dysfunctions in terms of poor attention and concentration, confabulation and constipation and caused by chronic depletion of vitamin B₁ attributable to multiple etiological pathways. KS co-occurs with HG, WE as WKS, akinetic mutism and dementia [34,57,75,143]. KS accounts for 10% of dementia and often preceded by an episode of WE but this is not always the case; however WKS is attributed to multiple factors

including most importantly thiamine deficiency and chronic alcohol abuse [34,75,143]. KS arising from HG is an uncommon happening and often misdiagnosed and under-diagnosed condition. A high index of suspicion through the lens of global amnesia and confabulation enables early recognition and, hence, prompt treatment that results in reduction in maternal morbidity and mortality and better outcome of pregnancy. Thiamine replenishment together with adequate fluid intake, electrolyte balance, elimination of predisposing factors, continuing monitoring and regular followup should be performed until patient is asymptomatic. In sum, non-alcoholic KS with overall amnesia caused primarily by thiamine deficit in pregnant patients with HG or WE takes a downhill course with possible permanent neurological disabilities, institutionalization, and early death when KS/WKS is not straightaway managed by thiamine treatment and supportive measures [75,143,144].

This critical review has some limitations including selection and publication biases, because a large number of articles published in closed access journal were not accessible. The accessibility of the relevant studies published in open access journal was also restricted due to high price tag. We also did not attempt to trace unpublished studies by contacting their authors. Despite all these barriers, we synthesize the data from the most influential accessible articles including case reports and systematic reviews and meta-analysis for this critical review. The strength of this study is that it addresses the most important research avenue concerning women's health in pregnancies. This review may enhance globally the awareness of sequential syndromes and fill the knowledge gap of professionals providing therapeutic services to pregnant women developing nausea and vomiting of pregnancy, hyperemesis gravidarum, Wernicke's encephalopathy, Korsakoff syndrome and Wernicke-Korsakoff syndrome. Finally our team suggests a new collective term for these conditions as "B₁ sequential syndromes" because prime cause and clinical picture are shared by these disorders and so treatment interventions (Figure 2).

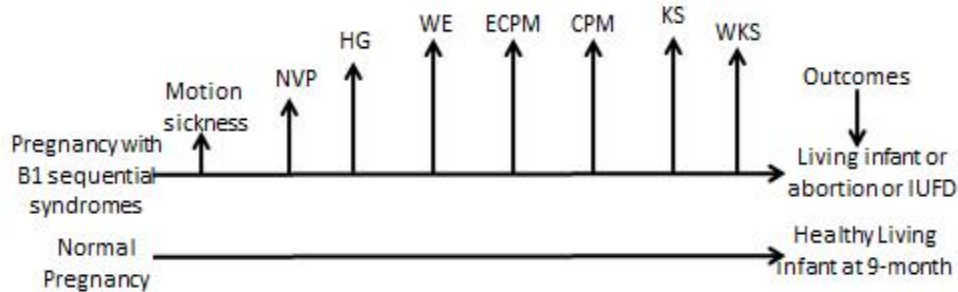


Figure 2. Normal and complicated pregnancy with B1 sequential syndromes and obstetric outcome (IUFD=Intrauterine fetal death)

Conclusion

Pregnancy is a normal physiological condition with increasing metabolic demand and hormonal changes and progresses to normal delivery ending at 9-month with live infant. However, certain vulnerable pregnant women may progress to developing morning sickness, nausea and vomiting of pregnancy, hyperemesis gravidarum, Wernicke's encephalopathy, Korsakoff syndrome and Wernicke-Korsakoff syndrome. The prime common cause underlying these sequential syndromes is acute or chronic thiamine deficiency but a variety of other etiological and risk factors are evoked to explain the pathophysiology of individual syndrome; however, till now these syndromes remain poorly understood including the role of inflammatory processes in hyperemesis gravidarum [145]. From diagnostic perspective and also ruling out comorbid diseases, each pregnant patient with or without any of these conditions needs clinical workup, laboratory tests, abdominal Ultrasound, brain CT scan, MRI and severity assessment of nausea and vomiting using specific scales. Once the diagnosis of HG or WE or KS is confirmed by exclusion, treatment with adequate doses of thiamine should be started on time and supportive measures should direct towards correction of electrolyte, fluids and other vitamins. Most pregnant patients with NVP, HG, WE, KS and WKS tend to improve with multimodal treatment to be continued till the successful delivery; however, a variable number of patients continue to

show residual features especially concerning WE, KS and WKS. Future studies should focus on strategies as how to globally define these sequential syndromes, develop universally accepted diagnostic criteria for early identification, explore inflammatory markers and improve robustly the maternal morbidity and fetal outcome.

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