Women's Health & Gynecology

ISSN: 2369-307X

Case Report

Mortality Secondary to Hyperemesis Gravidarum: A Case Report

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This article was published in the following Scient Open Access Journal:
Women's Health & Gynecology

Received September 23, 2015; **Accepted** October 27, 2015; **Published** November 09, 2015

Abstract

Background: Until the 1950's, maternal deaths were commonly caused by Hyperemesis Gravidarum (HG) [1]. Although maternal mortality secondary to HG has since decreased, herein we report a death occurring in the United States.

Case: We review a case of maternal death secondary to HG and resulting malnutrition.

Conclusion: Prompt treatment with parenteral vitamins, nutritional support, and methodical electrolyte replacement can prevent HG-related deaths. Clinician education and treatment protocols should be updated to proactively address the nutritional and metabolic requirements of pregnant women presenting with nausea, vomiting and malnutrition.

Keywords: Hyperemesis gravidarum, Pregnancy, Wernicke's encephalopathy, Pontine myelinolysis, Osmotic demyelination, Thiamin, Thiamin deficiency, Hyponatremia, Hypomagnesia, Malnutrition, Mortality

Introduction

Hyperemesis Gravidarum (HG) occurs in 0.3-10.8% of pregnancies, and leads to significant weight loss, malnutrition, dehydration, dysionemia, and ketonuria [2-4]. HG contributes to over 375,000 ER/hospital discharges in the US annually [5], and is associated with morbidity such as pneumomediastinum [6-10], renal failure, liver dysfunction, Boerhaave's syndrome, and Wernicke's encephalopathy [11-15]. HG is also associated with an increased risk of adverse outcome including low birth weight, neurodevelopmental disorders, intrauterine growth restriction, preterm delivery, and fetal and neonatal death [16-19].

Creanga, et al. recently reported that maternal deaths are on the rise in the United States, with 3,358 pregnancy-related deaths between 2006 and 2010 [20]. Approximately 20% of those are undelivered and potentially HG-related. However, since cardiac arrest or respiratory failure may be the primary cause of death, HG-related deaths remain essentially undocumented.

Here we report on the progressive deterioration of a woman with HG who developed profound malnutrition and electrolyte disturbances, and whose neurological signs were undiagnosed and improperly treated leading to her death.

Case

Week 3: Embryos transferred in a healthy 34 year-old 5' 7" 122 pound G1, P0 woman.

Week 7: Ultrasound confirmed viable twin pregnancy.

Week 9: Patient presented to ER with severe dehydration, unsteady gait, weakness and "off" affect. She complained of poor intake for 3 weeks and weighed 108 pounds. One liter of D5LR was infused over 40 minutes, then 1L normal saline (NS), followed by continuous NS at 150 ml/hr until discharge. Days 2-3, she exhibited slowing speech, confabulation and confusion with halting speech and possible hallucinations. Labs showed severe ketonuria and hematuria, and hypokalemia (3.1 mEq/L). Day 4, serum sodium (Na) was 130 (normal 133-148 mEq/L), potassium (K) 3.7 (normal 3.6-5 mEq/L), and blood urea nitrogen (BUN) 1 (normal 7-12 mg/dL). Patient complained of head and abdominal pain. She was discharged with a diagnosis of depression and hyponatremia, prescribed ondansetron and prenatal vitamins (Premesis Rx), and instructed to increase protein and salt intake.

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Week 10: The following day, her husband found her incoherent and incontinent in fetal position on the floor, and rushed her to the hospital. She was hypertensive, emaciated, disoriented, weak and unable to follow commands. Reflexes were brisk. Labs revealed hyponatremia (122 mEq/L), serum hypo-osmolality (269 mOsm/kg), normokalemia and proteinuria. Her serum vitamin B1, B6 and B12 levels were normal. Methylprednisolone and acyclovir were administered until infectious and autoimmune tests returned negative.

During the week, she was described as uncooperative, lethargic, non-verbal, flat, disoriented, and severely weak, with garbled speech and frequent staring. She developed nuchal rigidity, photophobia and headache for three days. Her EEG showed abnormal slowing of background patterns in the theta range. Midweek, she demonstrated a Babinski reflex, and was agitated and easily startled. It appeared that she was hallucinating, and had slow, halting speech. She was hypertensive and tachycardic with poor skin turgor. Treatment was fluid restriction and diuretics for hyponatremia, and medications for atrial arrhythmias and hypertension. A MRI of her brain revealed white matter hyperintensity in the periventricular regions, brainstem, cerebellar cortex, and hypothalamus.

At week's end, she weighed 98 pounds (>20% loss since IVF). She responded minimally with incomprehensible speech. Serum alanine aminotransferase (ALT) was 37 U/L (normal 3-23 U/L), albumin 0.7 g/dL (normal 3.1-5.1 g/dL), phosphorus 2.5 g/dL (normal 3.1-4.6 mg/dL), BUN 2 mg/dL, K 4 mEq/L, and Na 120 mEq/L.

Week 11: Due to inability to move, paucity of speech, brisk reflexes, clonus, hyperesthesia, and somnolence, she was transferred to a tertiary hospital. Her cerebrospinal fluid (CSF) protein level was elevated at 122/mg/dL. Her serum electrolytes remained depressed. She was cachetic and contracted. Parenteral thiamin, antibiotics, and methylprednisolone were administered. She became normonatremic, but exhibited photophobia, dysphagia, confusion, and clonus. Two fetal heart tones were confirmed.

A repeat MRI found bilateral signal abnormalities in the cerebral hemispheres, in addition to the brainstem, cerebellar white matter and corpus callosum. Neurology suggested a diagnosis of reversible Wernicke's encephalopathy (WE) or central pontine myelinolysis (CPM).

Week 12: Patient was mostly nonverbal and alert but disoriented. Tachycardia with atrial arrhythmias and dysphagia continued. Parenteral nutrition (PN) with standard multivitamins commenced. She became less responsive and startled easily. A repeat MRI was essentially unchanged. Neurology revised their diagnosis to extrapontine myelinolysis (EPM). Methylprednisolone and thiamin were discontinued. She was given anticoagulants, antibiotics, and folic acid.

Week 13: Patient became unarousable and nonresponsive with posturing. Her urine output decreased markedly, while her Na fluctuated near 140 for five days then gradually decreased to 133. She remained tachycardic and weighed 113 pounds. Neurology noted pathologically brisk reflexes in her upper extremities and lower extremity withdrawal, thus concluding a diagnosis of WE due to nutritional depletion and electrolyte imbalance. Parenteral thiamin was restarted. EEG monitoring revealed seizure activity. PN was replaced with enteral nutrition via a percutaneous endoscopic gastrostomy tube. Fetal heart tones were detected.

Week 14: Patient's weight dropped to 106.4 pounds, over 15% below her prepregnancy weight. Ultrasound detected two fetal heartbeats. Her EEG showed a steady sleep state. On day 36, the patient had respiratory failure. The autopsy concluded a differential diagnosis of diffuse leukoencephalopathy.

Wernicke's Encephalopathy

Reports of WE secondary to HG are on the rise, with over 25 cases published between 2012-2015 [15,21-43]. Recent studies show advances in the diagnosis and management of WE [42,44], nevertheless, 71-85% of WE cases remain undiagnosed until postmortem evaluation [45,46].

WE is typically identified by the symptom triad of ataxia, confusion and oculomotor abnormalities. However, 10-47% of patients lack these signs, especially with gradual or episodic WE onset, and non-alcoholic patients [45,47-49]. This patient lacked expected oculomotor signs likely because she received intermittent thiamin which can resolve symptoms within six hours [49].

Persistent or prolonged vomiting, confusion, and unintentional weight loss are red flags indicating a high risk of WE [50]. Additional WE signs seen in this patient include weakness, dysarthria, confabulation, akinetic mutism, aphasia, cardiac failure, seizures, abdominal pain and nausea [51-55]. Mental status changes are nearly universal and exhibited as dizziness, drowsiness, apathy, and cognitive impairment [46,52]. Gait abnormalities range from weakness to inability to stand [52], and may be somewhat difficult to identify in HG patients experiencing vertigo and postural hypotension.

WE develops rapidly when initiated by severe, short-term thiamin deficiency (TD) in the presence of infection [45] or an event that rapidly increases thiamin requirements [56]. Chronic WE associated with HG occurs subsequent to persistent or recurring mild TD [56]. This gradual onset of WE manifests with nonspecific symptoms such as headaches, anorexia, irritability and abdominal discomfort, all common with HG. Then progresses to spastic paresis and myoclonus with nuchal rigidity, as seen in this patient [44,45,56].

As her condition worsened, advanced WE signs [49,56] were noted: elevated transaminase levels, diffuse background slowing on EEG, seizure activity, and high CSF protein levels. Consistent with the literature, her MRI findings involving the cerebellar and cerebral cortices, typically observed in non-alcoholic patients, correlated with poor outcomes [39,56].

Because WE is an emergency situation, it should be empirically treated with IV thiamin, along with electrolyte replenishment, elimination of predisposing factors, and implementation of nutritional support [56,57]. Baseline MRIs are important to diagnosis and evaluation of treatment, as parenteral thiamin may alter MRI findings within 2-3 days [49,56]. Unfortunately for this patient, antibiotics and nutritional intervention were not initiated for two weeks. Thereafter, treatment was inadequate and inconsistent. If thiamin administration had commenced

immediately, along with parenteral nutrition, chronic disability or death could have been prevented; the longer the delay, the poorer the outcome [46,58].

Thiamin

Thiamin is an essential micronutrient only obtained from food or supplements. The body's 25-30 mg of thiamin storage is depleted before three weeks of deficits, regardless of BMI [49,52,59]. TD predisposes patients to WE as thiamin is required for metabolism of glucose and maintenance of myelin in the brain [51].

TD is prevalent during pregnancy because the body redirects maternal thiamin to the baby, especially during later pregnancy, exacerbating maternal TD [39,60-65], and greatly increasing the risk of fetal loss and preeclampsia [39,51,60-64]. The recommended thiamin intake of 1.4-1.5 mg during pregnancy is inadequate for pregnancies with multiple gestations or HG [38,42,49,64,65]. HG patients require even more due to their high carbohydrate diet [61,66], coexisting deficiencies (e.g. Mg) [56,66], limited food variety, prolonged malnutrition, impaired absorption [38,67], and reduced muscle mass for storage. Symptoms of early TD mimic HG, including depression, irritability, weakness, headache, dizziness, insomnia, myalgia, muscular atrophy, anorexia, nausea, vomiting, weight loss, constipation, memory loss, pain sensitivity, and mood lability [58,68-70]. TD adversely impacts the fetus as well, increasing the risk of impaired brain development, neuromotor immaturity, cranial malformations, low birth weight, and IUGR [60,61,62,64,71].

TD also weakens cardiac function [68], and likely contributed to this patient's heart failure. Within 48 hours of discontinuing parenteral thiamin and receiving diuretics, which increase thiamin excretion [68-74], she developed atrial arrhythmias and refractory tachycardia. This patient's b-type natriuretic peptide (BN) test subsequently returned elevated at 868 pg/ml, suggesting moderately-severe heart failure, and a 15 times higher risk of death [73,74].

Confirmatory lab testing of TD may be confusing, as current testing reflects only 0.8%-10% of the body's thiamin stores and represents recent thiamin intake [68,69]. Further, thiamin testing is not always available or reliable, and researchers report 50% of WE patients have normal thiamin levels [49,50,68,75], suggesting multiple causative factors exist for WE.

Given the high prevalence of TD in pregnancy [61,63,71], TD should be assumed in patients with HG. Parenteral thiamin is non-toxic and rarely causes anaphylaxis, making proactive administration during pregnancy safe. Thus, immediate thiamin administration should be initiated in any patient with nausea and vomiting or other predisposing conditions, especially those receiving parenteral nutrition, diuretics, or glucose, and those with abnormal cardiac or neurological symptoms [56,68,72].

Of note, this patient's severe malnutrition was documented repeatedly without intervention, along with recent depression and anorexia subsequent to HG. Clinicians postulated her symptoms were an eating disorder or psychosis, and suggested she might want to terminate. Beginning pre-hospitalization, however, her neurological symptoms impaired self-feeding. In addition, she lost 10 pounds during her first two inpatient weeks. Parenteral nutrition with multivitamin infusion and folic acid was then instituted for 19 days, with IV thiamin intermittently administered on 11 nonconsecutive days [76,77].

Had she survived, her twins would be predisposed to TD, as approximately 85.2% of babies born to TD mothers are also deficient [61]. If breastfeeding, these infants develop TD within 3-4 weeks and have greater incidence of SIDS, behavioral changes, autism, delayed language development, and decreased visual alertness [60-64,71]. Addressing TD proactively during pregnancy not only benefits mothers, but also their infants.

Osmotic Demyelination Syndrome (ODS)

This patient's condition was further complicated by refractory hyponatremia, rapid correction of which often leads to myelinolysis. Resulting MRI changes develop over 1-4 weeks [51,78-88], however, partial healing may occur simultaneously with appropriate treatment, complicating the picture [47,82-92]. Achieving normonatremia is crucial as the presence of even mild hyponatremia increases mortality risk by 30%, regardless of comorbid conditions [83].

Patients with hyponatremia present with nausea and vomiting, headache, short-term memory loss, confusion, lethargy, fatigue, anorexia, muscle weakness, spasms, seizures, and decreased consciousness [84], all of which were seen in this patient. Because sodium and thiamin are interdependent, with thiamin involved in nerve impulse conduction, and its uptake dependent upon sodium, deficiencies in either can cause severe neurological sequelae [49,68,70].

Central pontine myelinolysis (CPM), or demyelination in the pons, is induced by slight increases in osmotic pressure attributable to electrolyte infusions, especially in the presence of severe infections, cachexia, and electrolyte imbalances [57,85]. This patient exhibited common signs: confusion, pseudobulbar palsy, dysarthria, dysphagia, and spastic paresis [54,78,86].

CPM is often biphasic, beginning with encephalopathic symptoms, followed by brief improvement, and then progression to signs of myelinolysis [78,85]. Similarly, this patient experienced neurological improvement with nutritional intervention and normonatremia, only to develop persistent dysarthria and dysphagia before becoming comatose and hyponatremic.

Lesions outside the pons, or extrapontine myelinolysis (EPM), are rare, affecting the cerebellum, basal ganglia, cerebral white matter, hippocampus, and the corpus callosum [78,77]. EPM occurs in approximately 10% of CPM cases, and was exhibited in this patient by cognitive deficits, seizures, tremor, myoclonus, and dystonia [54,88].

Demyelination occurring both within and outside the pons is termed ODS, and usually associated with significant osmotic shifts. In this severely malnourished patient, numerous osmotic shifts occurred due to alternating fluid restriction and rehydration, diuretics, PN, and electrolyte replacement. TD and cachexia left her with minimal osmolytes and inadequate amino acids for their production, thus increasing the probability of demyelination [78,88,89].

This patient exhibited signs of WE, CPM and EPM, all of which were suggested as possible diagnoses by her treating physicians, but were not considered as concurrent. Yet, ODS is reported to

accompany WE in about 30% of cases [78]. Proactive and more systematic intervention with nutritional therapy and electrolyte replacement would have improved the odds for this patient and her twins.

Discussion

This case presents the complexity and critical importance of proactively managing nutritional and metabolic imbalances associated with HG. Ultimately, this patient's nutritional deficiencies triggered not only cerebral vasogenic edema associated with WE, but also osmotic shifts leading to osmotic demyelination syndrome (ODS). This patient's course was further complicated by urosepsis, possibly confusing the clinical picture with septic encephalopathy and triggering WE [45]. Delayed diagnosis in addition to inadequate treatment and nutritional intervention resulted in her death.

Recently, five maternal deaths have been reported secondary to HG [40,41,91]. These cases were complicated by diagnoses including Wernicke's encephalopathy, seizures, hypokalemia, thyroid storm, dehydration, and/or severe thyrotoxicosis. In addition to our case, these fatalities illustrate the importance of rapid diagnosis, preventative vitamin supplementation, and electrolyte monitoring and correction.

To our knowledge there are eight previously reported cases of WE with ODS secondary to HG [42,43,47,92-96]. Maternal survival was 100%, although some suffered disabilities, however the fetal loss rate was 33%. Fetal morbidity is unknown. This report is the first to describe both maternal and fetal deaths due to the co-occurrence of WE and ODS secondary to HG.

Recommendations

Firstly, we recommend documentation and investigation of all HG-related deaths, including necropsies with detailed neuropathological examinations in those with neurological symptoms [56]. This patient's death was coded as "respiratory failure", and the autopsy listed cause of death as "diffuse leukoencephalopathy," thus obscuring the diagnosis of HG.

Secondly, we recommend prescribing prenatal vitamins which contain a minimum of 5 mg of thiamin to all pregnant women, especially those with nausea and vomiting and those carrying multiple fetuses [97,98]. PremesisRx prenatal, given to this patient, lacked thiamin. Further, all women at risk for HG, including those with a personal or family history of HG [99,100], should be prescribed prenatal vitamins and B complex preconceptionally to correct deficiencies.

Thirdly, given B vitamins are inexpensive, non-toxic, well-tolerated, widely available, and critical to maternal and fetal functioning, we recommend parenteral vitamins with 100 mg thiamin, immediately be given to all mothers presenting with vomiting, dehydration and/or weight loss, urgently if neurological or cardiac symptoms are present. Protocols should recommend infusing thiamin up to 1000 mg/day daily for 5 days to 3 weeks to replenish stores [42,51,53,56,82], or until oral intake resumes. Minimum doses of 250 mg are crucial for patients with prolonged HG, especially in late pregnancy when fetal brain growth is rapid [62,101].

Recent studies suggest it is not critical that thiamin be infused simultaneously with glucose [102]. However, if it is not given immediately, it might be delayed or never given [56,103]. We, therefore, continue to recommend concurrent administration [45].

Oral thiamin dosing should follow parenteral when an HG patient is asymptomatic, preferably with a thiamin derivative such as thiamin tetrahydrofurfuryl disulfide, which is more readily absorbed than thiamin hydrochloride [104-106]. Given its short half-life, thiamin should be taken at least twice daily for three months or more in 30-50 mg doses [33,56]. HG patients rarely tolerate prenatal vitamins or B vitamin supplements, making compliance challenging. Oral supplements containing only critical nutrients like thiamin and pyridoxine are alternatives.

Finally, we recommend serum electrolytes be checked on all patients with a history of nausea and vomiting to screen for deficiencies. The patient's state of hemoconcentration or hemodilution should be taken into account when interpreting the results. HG patients in a catabolic state may not show obvious signs of clinical deficiency [107-115]. Careful replenishment and ongoing monitoring should be performed regularly until patients are asymptomatic with adequate intake. Table 1 shows general guidelines for treatment of HG with respect to weight loss.

Guideline For Treating NVP With Consideration Of Weight Loss:
Wt loss <5% - Rehydrate**, evaluate needed lifestyle & antiemetic changes. Check serum electrolytes. Prescribe 30-50 mg oral thiamin as tolerated.
Wt loss 5%-10% - Rehydrate**, review antiemetic options, evaluate need for nutritional support, and consider midline IV for regular infusion of fluids. Check metabolic panel. Prescribe 30-50 mg oral thiamin as tolerated.
Wt loss >10% - Rehydrate**, run comprehensive labs to determine nutritional status, give parenteral vitamins including B complex daily, reevaluate antiemetic strategy & tolerability, consult with nutritional support regarding increasing protein and vitamins, esp. B vitamins. Consider midline for PPN, enteral nutrition (NG/NJ, PEG/PEJ), or a PICC for TPN. Prescribe oral thiamin after discontinuing PN/EN.
REMEMBER: Check thiamin content of parenteral multivitamins. MVI only has 6 mg thiamin. Parenteral B-complex usually has 100 mg of thiamin.
**Rehydrate using D5NS with an ampule of MVI plus 100 mg thiamin and folic acid, or Myer's Cocktail + 1 ampule of MVI and folic acid, or a Banana Bag with B-complex. Additional nutrients such as vitamin K [108], zinc, selenium, iron, magnesium and calcium are likely deficient; replenishment benefits mother and baby and may preempt additional complications [109,110].

Table 1: Guidelines for treating HG.

Predisposing Factors For Thiamin Deficiency
Diuretics [111]
PN/Refeeding [15]
Malnutrition [65]
Hypomagnesia [66]
Inadequate thiamin intake [112]
Protein deficiency [113]
Vomiting/HG [37]
Pregnancy [56,61]
Malabsorption [38,114]
Antibiotics [115]
Antacids [56,112]
Cachexia [65]
Multiple Gestation [39]
Glucose Infusion [53]
Anemia [106]

Table 2: Predisposing Factors for Thiamin Deficiency.

Education

Additionally, we recommend all patients with nausea and vomiting be screened for TD, WE and ODS, and their caregivers and clinicians, especially obstetric and emergency personnel, be educated on the signs and management of these disorders. Table 2 lists predisposing factors for TD as were seen in this patient.

These actions, along with proactive parenteral vitamins and electrolytes as needed, should dramatically reduce neurological and cardiac sequelae secondary to HG, as well as associated morbidity and mortality.

Conflict of Interest

The authors report no conflict of interest.

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