Original Research Article

Title: Hyperemesis gravidarum, Wernicke's encephalopathy and Korsakoff syndrome looked through the lens of three cases, Paper II.

Running Title: Hyperemesis gravidarum

Abstract

Objective; Pregnancy a normal physiological condition is worsened by morning sickness, nausea and vomiting of pregnancy, hyperemesis gravidarum, Wernicke's encephalopathy and Korsakoff syndrome in vulnerable women with gestation. **Objective:** This report of three cases described hyperemesis gravidarum, Wernicke's encephalopathy and Korsakoff syndrome in the worsening pregnancies**. Method:** Prospective collection of data concerning three pregnant patients seen in Dubai Health Care City, Dubai, United Arab Emirates. **Results:** All three patients were admitted to the hospital with manifestations of HG and WE and one of them showed additional features of Korsakoff syndrome. One patient developed intractable hyponatremia and central pontine myelinolysis. Two patients developed abortion while one patient's pregnancy ended with successful delivery with living infant. All patients were managed with thiamine, antiemetics, parenteral fluids and electrolytes and one patients required steroid therapy. **Conclusion:** The findings of these cases are compatible with international literature on HG and its sequential syndromes. This study may enhance awareness of HG, WE and KS and also fill the knowledge gap of professionals providing services to women with worsening health during pregnancy in Arabian Gulf countries.

Keywords; Nausea and vomiting of pregnancy, Hyperemesis gravidarum, Wernicke's encephalopathy, Korsakoff syndrome, thiamine

1. INTRODUCTION

Pregnancy is a normal physiological condition that ends at nine month with a healthy born infant. However, vulnerable pregnant women are liable to develop morning sickness, nausea and vomiting of pregnancy (NVP), hyperemesis gravidarum (HG), Wernicke's encephalopathy (WE), Korsakoff syndrome and Wernicke-Korsakoff syndrome (WKS) during the progression of pregnancies [1.2]. HG is an emergency condition that affects 0.3-3 % of all pregnancies [3]. NVP occurs in 50% to 90% of all gravida and its onset 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 and may progress to HG [2-5]. HG characterized by pernicious nausea and vomiting, dehydration, electrolyte and fluid imbalance, weight loss, and ketonuria and necessitates hospital admission [2,3]. Hundreds of cases and studies have reported HG,WE, WKS and central pontine myelinolysis (CPM) in the literature with marked variability in clinical picture, laboratory findings, response to treatment and fetal offspring and maternal outcome [5-10]. The etiology of HG is multifactorial and its pathophysiology is not yet fully understood [5-7,11]. Furthermore, HG is reported to be aggravated by diverse co-occurring systematic diseases, surgical complications, WE, KS, and WKS, and needs multimodal approach including surgical interventions [12-17]. HG a prime cause of acute thiamine deficiency if not treated effectively progresses to WE, KS, WKS and CPM. Overall, only a small proportion of vulnerable pregnant women with or without prior thiamine deficiency tend to develop aforesaid sequential syndromes [5] requiring emergency admission to the hospital, immediate interventions with thiamine, antiemetic medications, electrolytes and fluids with regular followup till the end of pregnancy.

1.2 Aim of the study

The aim of this report was to describe three cases of hyperemesis gravidarum, Wernicke's encephalopathy, Korsakoff syndromeand Wernicke-Korsakoff syndromeand discuss the observed results in the light of international literature. The relevance of this study is

that there is scanty literature on worsening pregnancies in the Eastern world especially Arabian Gulf countries. This report may enhance health professionals' awareness and also fill up their knowledge gap concerning pregnant women with adverse pregnancies.

2. METHODS

Three cases under consideration were seen in the emergency room of Sulaiman Al-Habib Hospital, Dubai Health Care City in Dubai in year 2018/2019 and were admitted to the hospital for a variable timeline. The relevant data including sociodemographic and clinical variables together with given treatments were prospectively collected on a semistructured proforma. All the cases were evaluated and managed by one of the co-authors. All the patients gave oral consent for publication of their data in the journal provided their personal identities were kept confidential. We seek the permission from the director of the hospital to publish the data of these cases. The following are the clinical details of individual patient.

3. RESULTS

3.1 Case Vignettes

3.2 Common Denominators: Three Cases

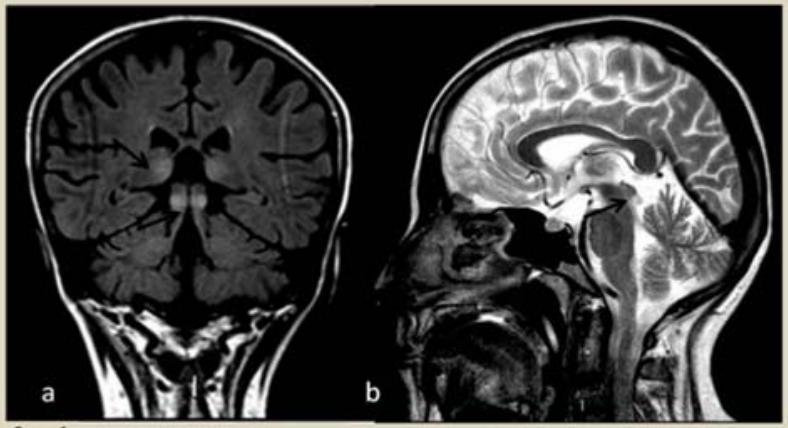
Three multigravida pregnant women presented with moderate to severe nausea and vomiting along with other variable signs and symptoms of uneven duration and were managed with multiple treatments. All patients had previous history of hyperemesis gravidarum without any complications. All women were admitted to the hospital for short period (less than 15 days) and discharged in stable state.Prior to admission, all patients reported nausea and vomiting of one to two weeks and consulted doctors in other hospitals who prescribed parenteral fluids and antiemetic medications but of no avail. Two patients (case 2 and 3) were diabetic and hypertensive and their blood sugar and blood pressure were optimal and their prescribed medications were discontinued as both parameters were monitored on daily basis in the hospital. All patients were treated with recommended dosesof parenteral thiamine (50mg to 500mg/day), parenteral fluids and electrolytes and showed considerable clinical improvement. Based on given history,

laboratory tests, abdominal ultrasound and brain magnetic resonance imaging (MRI), a number of systemic diseases including odor disorders were excluded [5,18.].(Table.1). Three cases also reported intense pain in flanks and abdominal wall reflecting the severity of intractable NVP, HG and WE [15], and these symptoms rarely complained by pregnant patients or explored by physicians and, hence, unreported in the literature. Finally, all pregnant patients with persistent nausea and vomiting, dehydration, weight loss and poor nourishment needed referral to internal medicine and nutrition division in order to exclude or treat systematic and nutritional diseases.

3.3.1. Case 1

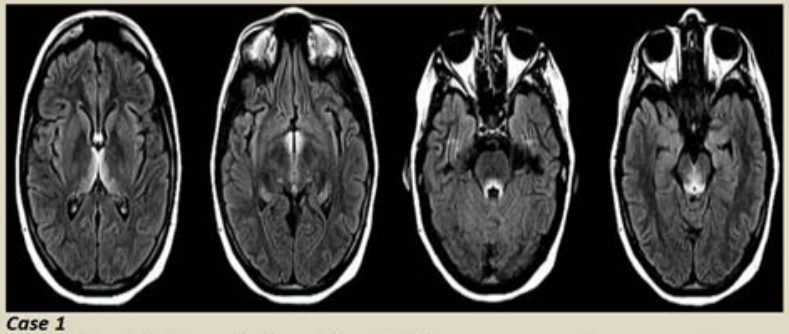
A 35-year-old patient with 7-week pregnancy and weight loss of 4 kg presented to emergency services with severe nausea and vomiting, loose motions, malnourishment, confusion, mild fever, slurred speech, ataxia, nystagmus and blurring of vision since 4 weeks. The patient was treated with intravenous fluids for hyperemesis gravidarum in another hospital without much improvement during the previous 4 days. On examination, the patient was awake, restless, confused, responding verbally, following one step commands on repeated verbal stimuli and restricted extra-ocular movements. The muscle tone was increased in all four limbs. Power was 4/5 and 3/5 in both upper and lower limbs, respectively. The muscle stretch reflexes were 4/5 in all four limbs. Laboratory investigations showed hemoglobin of 11.2g/dL, total leucocytes count (WBC) of 11.2 per microliter of blood with 40% lymphocytes (Normal value=20% to 40%). Urine report showed a leucocyte count of 10 per high power field [HPF] (normal 0-5wbc/HPF) and positive nitrite, both indicators of mild infection. Other tests including platelet count, urea, and creatinine were within normal limits except low sodium and potassium. Ultrasound of abdomen showed single intrauterine living fetus. Brain MRI showed bilateral and symmetrical hyperintense signal alteration at the level of the medial portion of the thalami and tectal plate (Figure 1). This patient was diagnosed with hyperemesis gravidarum and Wernicke's encephalopathy. Adequate doses of thiamine 50 to 500mg IV were first given for few days followed by parenteral fluids with multivitamins and correction of sodium and potassium. No antibiotic was used because parenteral fluids maintained adequate hydration and values of blood leukocytes returned to normal level with negative nitrite dipstick test. At discharge, the patient was stable and was prescribed thiamine 50mg daily orally along with dietary supplements. The patient

had regular followup with no complains. However, she developed intrauterine fetal demise (IUFD) at 15 weeks, and fetus was removed medically. She was discharged in stable condition and was advised to take multivitamins and nutritious diet.



Case 1

35-year-old woman, in her 7 weeks of gestation: coronal FLAIR (a) and sagittal T2-weighted (b) MR images showing bilateral and symmetric hyperintense signal alteration at the level of the medial portion of the thalami and of the tectal plate.



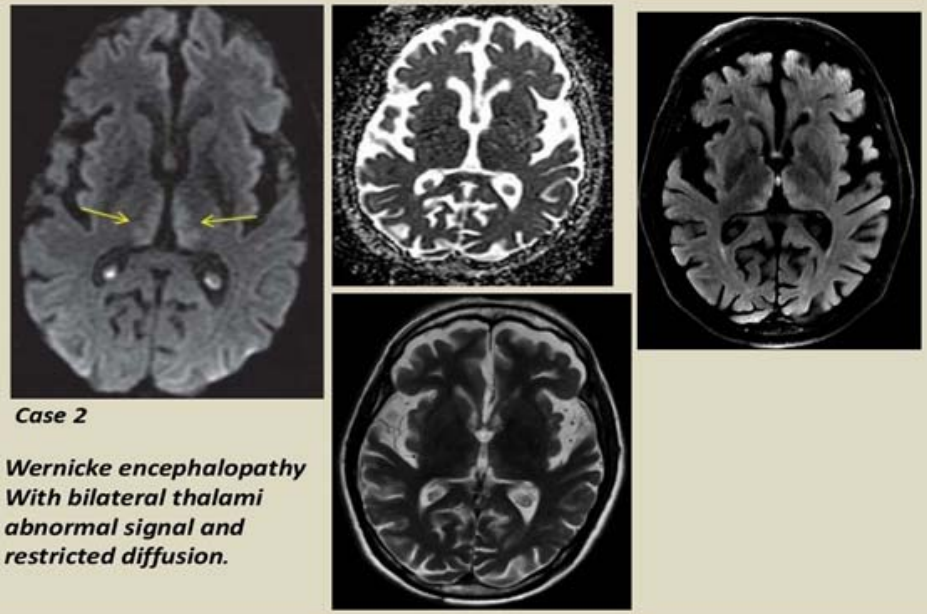
Case 1

Wernicke Encephalopathy: MRI in a seven weeks pregnant woman with recent mental status change, repeated vomiting, and weight loss. Axial FLAIR shows abnormal bright signal.

Figure 1MRI findings of Wernicke's encephalopathy

3.4 Case 2

This 38-year-old woman with 9-week gestation developed severe nausea and vomiting associated with 8 kg body weight loss over the past 3 weeks. On examination, she showed dehydration, weakness, confusion, and nystagmus together with mild hepatic failure. Four days after starting intravenous dextrose with vitamins, she developed temporary memory loss, confusion, ataxia, dysarthria, and mild left upper motor neuron facial weakness. Thiamine 200mg to 500mg was given IV for three days and, thereafter, no further deterioration was observed. MRI of the brain showed bilateral abnormal signal and restricted diffusion in thalami (Figure 2). The intensity of nausea and vomiting reduced but persisted until the early IUFD at week 14. The dead fetus was expelled using medical intervention. Subsequently, her condition gradually improved. In this case, intractable HG was complicated by acute WE and KS attributable to excessive intravenous dextrose load given before thiamine replenishment. The association of HG with rapid intravenous calorie load leading WE and KS is reported in the literature [19].



Case 2

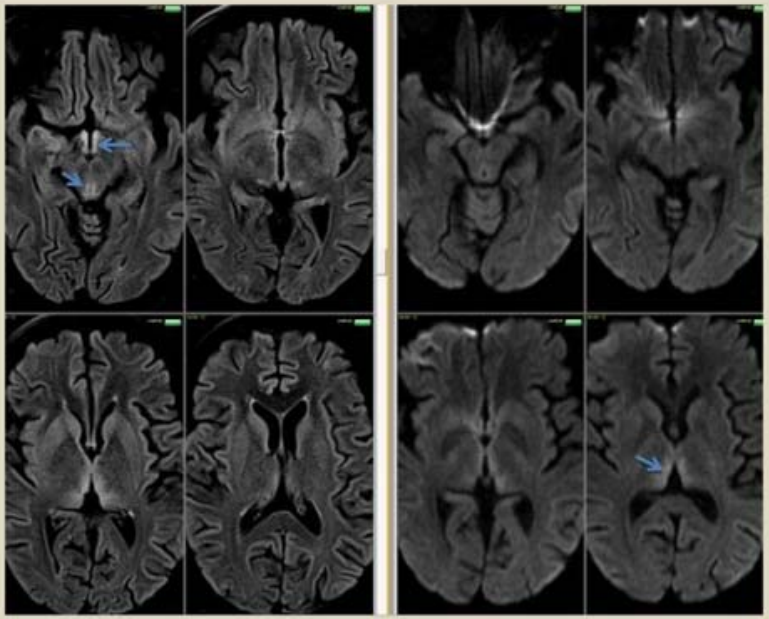
Wernicke encephalopathy With bilateral thalami abnormal signal and restricted diffusion.

Figure 2 MRI findings in Wernicke's encephalopathy

3.5 Case 3

A 39-year-old woman with 6-week pregnancy presented with severe nausea, vomiting, weakness, dehydration, confusion, and unsteady gait since 2 weeks. Laboratory investigations showed hypokalemia 3.0 mEq/L (normal 3.6-5 mEq/L), hyponatremia 128 mEq/L (normal 133-148mEq/L) and severe ketonuria. Complete blood count was normal. Her reflexes were brisk. On examination, she was uncooperative, lethargic, non-verbal, flat affect, disoriented, malnourished, weak, and dehydrated. MRI of brain revealed bilateral symmetrical (FLAIR) hyperintensity with some diffusion restriction in dorsomedial thalami, mammillary bodies and periaqueductal area (Figure 3). Liver function tests including serum alanine aminotransferase (ALT) was 37 U/L (normal 3-23 U/L). Serum albumin was 0.7 g/dL (normal 3.4-5.4 g/dL). Phosphorus was low, 2.3 g/dL (normal 2.5-4.5 mg/dL). Blood urea nitrogen was 2 mg/dL (7-20mg/dL). This patient was diagnosed with hyperemesis gravidarum and Wernicke's encephalopathy. She also developed severe refractory hyponatremia associated with nausea and vomiting, headache, short-term memory loss, confusion, lethargy, fatigue, anorexia, muscle weakness, spasms, and seizures with decreased consciousness. Parenteral thiamine up to 300mg/day for 5 days and methylprednisolone (60mg/day for 48hours, then slowly tapered off over one week) were administered. Her condition improved but exhibited photophobia which resolved later without any intervention. The refractory hyponatremia most likely due to rapid parenteral fluid was managed successfully using hyponatremia guidelines [20]. However, this patient manifested signs and symptoms of CPM or also called osmotic demyelination syndrome (ODS) may be due to rapid correction of sodium deficiency. CPM was managed successfully, though it is an irreversible condition [21,22]. This patient delivered a living infant at 35-week of pregnancy and was discharged in stable condition.

Case 3



Wernicke encephalopathy in a 39 year-old woman who had severe hyperemesis gravidarum. Axial fluid-attenuated inversion-recovery and Diffusion weighted MR image shows bilateral symmetrical FLAIR hyperintensity with some diffusion restriction in dorsomedial thalami, mammillary bodies and periaqueductal grey (arrows)

117 Figure 3 MRI findings in Wernicke's encephalopathy

Table 1. Sociodemographic and clinical features of 3 cases

Patient	1	2	3
Age in years	35	38	39
Gravida	3	4	4
Gestation (weeks)	7	8-9	5-6
Duration of vomiting before presentation (weeks)	4	3	2-3
Weight loss	4kg	8kg	3.5kg
Dehydration	Yes	Yes	Yes
Flank and abd. wall pain	Yes	Yes	Yes
Smoking consumption	None	None	None
Alcohol consumption	None	None	None
Comorbid Medical diseases	None	T2DM with high BP	T2DM with high BP
Laboratory finding			
Thiamine level	Low	Low	Low
Liver function test	Normal	Elevated	Elevated
Amylase, Lipase	Normal	Normal	High
Hemoglobin	11.2g/dl	10.0g/dl	11.7g/dl
Electrolytes	Low Na and K	Low Na and K	Low Na and K
Ketonuria	Marked	Marked	Marked
Neurological Finding			
Cognitive Impairment	Irritable with impaired recent memory and confusion	Disoriented to time and impaired recent memory	Drowsy, confused and restless
Ataxia	Slight	Marked	Marked
Nystagmus	Present	Present	Present
Muscle tone	Marked	Marked	Marked
Reflexes	Brisk	Brisk	Brisk
Ultrasound of Abdomen	Normal	Gallbladder sludge	Gall bladder stones
Ultrasound of Pelvic	No molar or multiple pregnancy	No molar or multiple pregnancy	No molar or multiple pregnancy
MRI of brain			

	Bilateral and symmetric hyperintense signal alteration at the level of the medial portion of the thalami and of the tectal plate.	Bilateral thalami abnormal signal and restricted diffusion.	Bilateral symmetrical FLAIR hyperintensity with diffusion restriction in dorsomedial thalami, mammillary bodies and periaqueductal area.
Treatment			
Respond to Thiamine	Yes	Yes but partial	Yes
Antiemetic	Yes	Yes but partial	Yes
Parenteral fluids with vitamins	Yes	Yes with adequate hydration	Yes
Condition on discharge	Stable	Stable	Stable
Neurological complication	None	None	Mild ataxia
Pregnancy outcome			
	Early intrauterine fetal death (IUFD) at 15 weeks	Early IUFD at 14 weeks	Delivery at 35 weeks
Possible diagnoses	HG and WE	HG,WE and WKS	HG and WE, hyponatremia and CPM?
Average age (in years)=37.3; Gravida=3-4 range; Gestation (weeks)=3-4 range; duration of vomiting (weeks) =3.2 average; Average Hb=10.9gm/dL; Fetal outcome=67% death; Maternal outcome: no residual features with no death; T2DM=Type 2 diabetes mellitus; Antiemetic=dimenhydramine 25-50 mg every 6-8 h, then whenever needed.			

4. DISCUSSION

This report of three cases described hyperemesis gravidarum, Wernicke's encephalopathy, and WKS developed in vulnerable women at different timeline of gestation. Case 1 showed signs and symptoms of HG and WE along with mild infection and low levels of thiamine, sodium and potassium. Furthermore, abdominal ultrasound showed living fetus and MRI findings further supported the diagnosis of Wernicke's encephalopathy. This patient was managed by adequate doses of thiamine, antiemetic medications, correction of electrolytes and parenteral fluids with considerable improvement, and this clinical, diagnostic and management scenario is compatible with many cases reported in the literature [2,5,16,23]. This patient prior to admission to the hospital was possibly mismanaged for four days at other hospital as the condition of this patient did not improve. The implications of this case include the following; clinicians working in peripheral hospitals and by extension primary healthcare centers (PHC) need to early identify pregnant women with HG and WE and manage promptly with thiamine first and then other supportive measures including adequate

hydration. Second, pregnant mothers should immediately consult hospital emergency services or the nearest PHC when the fetal movements become feeble in order to prevent the early or late IUFD as happened in this case. However, in addition to other severe psychophysical burden, 50% pregnancies with HG and WE result in either abortion or early/late fetal demise, and 3% maternal mortality in deteriorating pregnancies [7,24-26].

Case 2 developed signs and symptoms of resistant HG along with WE and WKS as management with multiple therapies resulted in partial improvement. Administration of intravenous dextrose with vitamins prior to thiamine infusion worsened this patient's condition and she slipped into WKS. Furthermore, despite use of thiamine and use of antiemetics, nausea and vomiting did not stop possibly resulting in early IUFD. However, consequently mother showed considerable improvement and was discharged in stable condition with low moods. The sequential occurrence of intractable HG, WE and WKS is reported in the literature and multimodal approach including use of steroids tends to improve difficult-to-treat HG complicated by WE or WKS [5,7,15,25]. Presumably, there might be multiple causes of fetal demise in this patient including subtherapeutic or very high doses of thymine, comorbid diabetes mellitus and hypertension, uncorrected electrolyte imbalance, use of dextrose prior to thiamine, and no use of steroid therapy. Although sixth nerve palsy linked with intractable WE is reported in the literature [27], mild facial paralysis is an atypical finding in this case, might be due to unknown cause or unrecognized CPM. This case informs that dextrose should not be given in severe HG prior to thiamine administration as thiamine is utilized in dextrose metabolism and further reduces thiamine level and ultimately worsens HG and WE [28]. Consequently, the patient may slide into WKS as happened in this case and requires immediate intervention with multiple drug and nondrug therapies [29,30]. The outcome of pregnancy in this patient was early IUFD, and mother was mildly depressed with low moods and anxiety. The role of anxiety and depression in intractable HG is controversial and discussed extensively in the literature [7,25,31,32]; however most studies reported psychological disturbances being the sequelae of HG.

Case 3 presented with features of HG and WE and later developed refractory hyponatremia associated with possible CPM consistent with other studies [20,22,33]. She responded very well to thiamine, methylprednisolone, correction of acid-base imbalance and parenteral fluids with added vitamins. The pregnancy outcome was delivery of living infant at week 35 and mother was discharged in

stable condition. Evidently, like our case intractable hyponatremia a treatable condition is reported in severe HG associated with or without WE and rapid correction of hyponatremia is often the leading cause of CPM [20,22,34].. Sodium and thiamine are interdependent and thiamine is involved in nerve impulse conduction and its uptake dependent upon sodium. Therefore, deficiencies in either sodium or potassium or thiamine can cause adverse neurological sequelae including CPM [20,22,34,35]. Central pontine myelinolysis or osmotic demyelization syndrome (ODS) characterized by extensor planters, hyperreflexia, gaze palsies, spastic quadriparesis, confusion, spastic dysarthria or bifacial weakness (as also observed in case 2) was induced by increase in osmotic pressure attributable to electrolyte infusions especially in the presence of severe infections, cachexia, liver dysfunctions, hyperemesis gravidarum, hypokalemia and hyponatremia, and thiamine deficiency [20,22,33-35]. This patient also exhibited confusion, dysarthria, dysphagia and spastic paresis compatible with CPM, and was effectively managed by parenteral thiamine and methylprednisolone. Notably achieving normonatremia is crucial because even mild hyponatremia increases mortality risk by 30%, regardless of comorbid conditions [20,22,33-36]. Surprisingly, CPM is reported in a patient with normal sodium who recovered from Wernicke's encephalopathy [37]. Although the diagnoses of extra-pontine myelinolysis (EPM) and CPM are made by clinical signs and symptoms such as pseudobulbar palsy, pyramidal tract signs, depressed consciousness and radiological signatures, these diseases continue to challenge practitioners' skills across the board [38,39]. CPM is also reported in a pregnant patient with hypokalemia who presented with urinary incontinence, weakness and pain in lower limbs supported by MRI findings, which resolved completely at followup [35], though CPM is reported to be an irreversible neurological condition [21]. In our case, subsequent MRI was not done that might have helped in identifying CPM and its resolution with treatment. In sum, vulnerable patients with pregnancies develop variable clinical manifestations of sequential syndromes [5] and similarly the inconsistent responses to various interventions attributed to the uniqueness of individual pregnant patient and methodological differences.

Comment [MO1]: There is recent evidence that suggests that CPM is reversible if treatment is instituted See .early Rebedew DL. WMJ. 2016 Dec;115(6):326-8.

Now the question is why certain pregnant women develop sequential syndromes? Converging evidence suggests that a variety of etiological factors concerning maternal, fetal and external milieu determine the development of these diseases in the pregnancies [1-6,31,40]. These risk factors include but not limited to multigravida, multiple gestation, age, low education, psychosocial burden, molar

pregnancies, fetal maldevelopment, olfaction odors, non-availability of food varieties, nonsmoking, chronic alcohol use, thiamine deficiency, genetic loading, hormonal changes, increased metabolic demand, gut-brain dysfunctions, past history of HG, infection and inflammation, and nutritional deficiencies [1-6,31,40-44]. Our three cases showed some of these risk factors such as thiamine deficiency, age, fetal problems, no smoking, multigravida, genetic propensity, high metabolic demand and malnutrition. Equally important question is what are the pathophysiological pathways underlying these disorders of pregnancies? Many pathophysiological mechanisms underpinning these sequential disorders of pregnancy are identified yet these disorders are poorly understood [1-6,16,31,43-46].

This report of three cases has some limitations. The diagnosis of three cases was based mainly on clinical observations, laboratory tests and MRI typical findings. Both serum and urinary thiamine estimation is of diagnostic help but urinary thymine level were not done in our patients. However, thiamine concentrations are not specific to the diagnosis and may be normal in malnourished patients. Similarly, laboratory measures of blood transketolase activity and thiamine pyrophosphate may be of diagnostic help but were not available in our setting. The onset of nausea and vomiting started at very early stage of gestation, i.e., 3-5 weeks in our cases, and evidently most pregnant women develop NVP at 4-8 weeks of gestation. It is possible that we might have missed the diagnosis of NVP because of delayed consultation by our patients. Brain MRI was also not repeated to evaluate the progression and impact of treatment concerning sequential syndromes in our cases. Despite these limitations, the data on reported cases is compatible with international trends especially the variability and inconsistencies and highlight the importance of early health seeking by pregnant patients, timely diagnosis and prompt treatment of sequential syndromes including CPM to prevent potentially adverse consequences including fetal and maternal deaths in the worsening pregnancies.

5. CONCLUSION

In conclusion, morning sickness, nausea and vomiting of pregnancy are very common occurrences during pregnancy. Hyperemesis gravidarum, Wernicke's encephalopathy, Korsakoff syndrome and Wernicke-Korsakoff syndrome occur in decreasing frequency in

the worsening pregnancies, and share common symptoms and signs, etiologies and pathophysiological mechanisms, comorbidities, interventional approaches and outcome, though these are independent sequential syndromes. Each patient is unique in clinical presentation and needs personalized targeted therapies which would differ in many respects from other patients, and, hence, data variability is pervasive in reported cases across the world. Most patients with HG, WE and KS require hospitalization and multiple therapies, and intractable cases need short-term steroids. Co-occurring psychomedical conditions and serious medical complications tend to exacerbate clinical condition of pregnant women linked with poor fetal and maternal outcomes. Woman health is highly important and future research should direct towards tailoring universal definitions, diagnostic criteria, updated treatment protocols, and further elucidate underlying pathophysiological mechanisms of sequential syndromes of pregnancies in order to improve robustly fetal and maternal outcomes.

Consent for publication

Written consent from the patients was obtained.

Conflicts of interest

The authors reported no conflicts of interest.

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