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Gestational Malnutrition is Still the Skeleton in the Closet: Where Are the Malnutrition Risk Screening Criteria?

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ABSTRACT

In 2020 there were 3,613,647 live births in the US. Fifty to 90% of those pregnancies were affected by nausea and vomiting of pregnancy (NVP) while the most severe NVP, known as hyperemesis gravidarum (HG) affected 1.5-3.0% of those gravidas. In 2014 58,436 gravidas were hospitalized with HG. While hospital admissions for HG were down 42%, the number seen in Emergency departments rose by 27.7%. Although HG has been viewed as a positive predictor of a favorable pregnancy outcome, patients who also demonstrate weight loss and electrolyte disturbance may be a distinct entity and at greater risk for growth retardation and fetal anomalies. Poorly managed HG can result in compounded maternal injuries, increased rates of therapeutic abortions and suicide ideation, as well as a high rate of fetal loss. This study focuses on one of the most severe catastrophes originating from HG: Wernicke's encephalopathy (WE) continues to be an under-recognized and often misunderstood disease in all populations. The acknowledged cause of WE is vitamin B1 or thiamin deficiency, a specific form of malnutrition. Unfortunately, this syndrome is most often recognized at autopsy, especially among non-alcoholics.

One manifestation of WE is cognitive dysfunction which may explain the increase in suicidal ideation and/or elected terminations. The current mounting legislation of pregnancy termination limits will complicate the decision to abort for critically ill gravidas and their medical providers. However, antecedent events to WE are extremely poor nutritional intake leading to excessive weight loss and delayed nutritional interventions which can mitigate these situations.

Keywords

Malnutrition, Hyperemesis gravidarum, Catabolic gestation, Nutritional neglect, Fetal demise.

Introduction

In the 21st century, iatrogenic malnutrition exists even amid abundance [1]. This fact may resonate with disbelief as malnutrition is often thought relegated to those societies, which are resource-deprived due to famines, floods, lack of education and/or living under dictatorships [2]. In 1974, Dr. Charles Butterworth published an often-cited article "the skeleton in the closet" which described that 50% of hospitalized patients in the US were malnourished on admission and 75% of patients who were at risk, had worsening malnutrition during their hospitalizations [3]. After the Butterworth report, screening criteria for malnutrition were formulated for oncology patients, the acutely ill, the elderly, medical, surgical and trauma patients, pediatrics and prematurely born babies in neonatal intensive care units (NICU) [4]. However, to date, universal screening for malnutrition in pregnancy does not seem to exist.

Background

Of all the problems which arise in pregnancy one of the more dreaded is the uncontrollable hyperemesis gravidarum (HG) or the severe nausea and vomiting of pregnancy (NVP) which can begin as early as six weeks of gestation and continue throughout for 20% of sufferers [5,6]. Malnutrition was first formally identified in the HG population in 1995 by van Stuijvenberg, followed by others

[7-9]. Although HG has been viewed as a positive predictor of a favorable pregnancy outcome, those patients who also demonstrate weight loss and electrolyte disturbance may be a distinct entity and at greater risk for growth retardation and fetal anomalies [10]. Currently none of the malnutrition screening or assessment tools specifically includes the pregnant patient [11].

As a result, this population has suffered continued mortality and morbidity. The time has arrived to address that void. Hence, our goals in conducting this study are to:

1. Create awareness of the morbidity caused by malnutrition originating from HG and WE, to the fetus, the host and society.
2. Create screening criteria for "gestational malnutrition" by expanding a current malnutrition screening tool.

Methods

We began this investigation by using data from our previous study of 27 women with severe HG whose condition worsened into WE which followed the 2019 seminal systematic review by Oudman et al. of 177 cases [12,13]. We subsequently removed Stephens from this current review, as on closer inspection this report was included in the Oudman review, albeit the publication was cited "in press 2017" [14]. This then brought our post 2019 HG-WE case count to 26.

Then searching PUBMED with the MeSH terms "hyperemesis gravidarum" AND "Wernicke's encephalopathy", and the years of 2019-2023, we looked for additional cases not included previously. This yielded 51 articles. Of the publications which were eliminated: 4 were review articles; 26 were included in our 2022 paper; one described a termination at 10 weeks which subsequently developed WE and one was related to cancer; 3 were related to bariatric procedures; one described alcohol misuse; one case was published in French; two described schizophrenia; and 8 were new 2023 HG-WE cases, with one as a conference poster. Two cases we inadvertently missed from 2019; 3 from 2022 were published after our paper was submitted. These 13 new cases brought the published cases of HG-WE after the 2019 Oudman review to 39 gravidas and 41 fetuses in 30 reports from 12 countries. Descriptions of these cases are detailed in Table 1. (Descriptions of hospitalized pregnant women who HG, deteriorating into WE.)

Details of maternal outcomes are provided in Table 2 (Net weight loss by gestational age compared to the Institute of Medicine (IOM) recommended gains) and Table 3 (Electrolytes status of 14 gravidas with HG who presented with cognitive dysfunction). We provided supplementary information with Table 4 (Problems associated with low electrolytes) and Table 5 (Components of pregnancy (or the products of conception-POC) at term, 40 weeks.). Table 6 (Clinical data on cases of IUFD (intrauterine fetal demise) summarizes adverse fetal outcomes and will be explored in "Discussion".

Current malnutrition/nutrition screening and assessment tools were examined for components, which would offer the most comprehensive opportunity to incorporate specific characteristics unique to pregnancy into its criteria. These included the MNA-SF (mini nutrition assessment- short form), MST (malnutrition screening tool), MUST (malnutrition universal screening tool), Simple, 2 Part, NST/BAPEN (nutrition screening tool/ British Association of Parenteral and Enteral nutrition, NUTRIC (nutrition risk in critically ill), SNAQ (short nutrition assessment questionnaire), NRS-2002 (nutrition risk screening), SGA (subjective global assessment), the GLIM (Global Leadership in Malnutrition) criteria and the criterion developed by The Academy of Nutrition and Dietetics and the American Society of Parenteral and Enteral Nutrition (AND/ASPEN) [15-18]. The latter three are nutrition assessment documents.

We then reviewed the tools, which illustrate the weight gain recommendations of pregnancy issued by the IOM and fetal development. These data are displayed in Figure 1 (Weight gain by BMI and gestational age) and Figure 2 (Fetal development from conception to term) and will be covered in "Discussion".

Finally, we integrated criterion from a current malnutrition-screening tool along with information from Figure 1 to create a revised inclusive malnutrition-screening tool. The screening tool selected was assessed by this provider (ME) to be the most compatible for pregnancy integration and has been utilized by nutrition professionals since 2012 [18]. The revised and inclusive details are displayed and highlighted in Table 7 (Modified AND/ASPEN weight loss criteria for malnutrition, including pregnancy) and Table 8 (Modified AND/ASPEN energy deficit criteria for malnutrition, inclusive of pregnancy) and are found in Conclusions with our recommendations.

Results

Our current study investigated the outcomes of 39 pregnant women with HG which deteriorated into the metabolic crisis of WE and their 41 fetuses. This survey brings the known published cases of HG-WE women to 216 since 1955. Descriptions of hospitalized pregnant women with HG, deteriorating into WE are detailed in Table 1.

Discussion

HG and WE are described as "rare" events in publications. While we could find no numerical definition for "rare", to date the number of HG-WE cases totals 216. HG-related Injuries include the physical damage which is likely induced by the pneumatic forces of retching and vomiting which can result in splenic avulsion**,** esophageal rupture, and subluxation of the orbit, those due to severe dehydration manifesting in acute renal failure, deep vein thrombosis, pancreatitis, and those which result from gross under-nourishment, culminating in WE (a lack of vitamin B1, thiamin, magnesium, and phosphorus), hemorrhage and bleeding issues resulting from vitamin K deficiency, cardiac and respiratory arrest due to electrolyte deficiencies as well as death from extreme weight loss [50-66]. Prolonged hospitalizations of > 10 days were noted for 12/39 women (30%), totaling 262 days, or an average of 21.8 days per gravida. These are patients # 4,12,14, 15,16,18, 19, 23, 29, 32,34, and 36.

Table 1: Description of hospitalized pregnant women with HG, deteriorating into WE.

Patient #/ Author/year/ country, ref #.	Age Gravida/ Para	Gestation week	Height	Pre-gravid Wt.	Current Wt./Wt. loss	Weeks of illness and/or poor intake. Significant issues.
#1. Palakkuhyil 2019 India [19]	34-year-old G3P2	n/a	n/a	n/a	n/a n/a	The patient presented with visual loss, a 2-week history of HG, decreased food intake, ataxia and was diagnosed with optic neuropathy. Her ataxia persisted at discharge. Pregnancy outcome n/a.
#2. Aneja 2019 India [20]	20-year-old G1P0	23	n/a	n/a	n/a n/a	The patient presented at 23 weeks with a triplet gestation, excessive vomiting, and dehydration. On HD 10, 24.5-week triplets were born prematurely, weighing 508 g, 429g, 389 g. All succumbed to extreme prematurity. After delivery, the patient began vomiting after being given oral glucose by family, became irritable, confused, and unable to speak. She was noted to have ophthalmoplegia and quadriparesis. Serum electrolytes reported as normal with sodium at 132.7 mEq/dL and potassium at 3.5 mEq/dL. A septic screen was positive for cervical *E. Coli* which was treated. The patient recovered by 6 weeks postpartum.
#3. Mishra 2019 India [21]	30-year-old G1P0	21	n/a	n/a	n/a n/a	The patient was first hospitalized at 10 weeks for severe vomiting and re-presented at 16 weeks with continuous vomiting for 1 month and an unsteady gait. Electrolytes were reported as normal. The patient was transferred to the reporting facility with confusion and bilateral nystagmus. She again re-presented at 19 weeks with vomiting and provided thiamin but experienced poor compliance due to nausea and vomiting. At 21 weeks she again re-presented with insomnia, auditory and visual hallucinations, and was diagnosed with Korsakoff psychosis. She was treated with anti-psychotics and thiamin. An elective cesarean section was performed at 36 weeks for oligohydramnios, delivering a SGA 2.25 kg female neonate. At 36 weeks an AGA female infant is expected to weigh approximately 2.62 kg. Postpartum, the patient continued with memory deficits.
#4. Ahmed 2020 Qatar [22]	32-year-old G/P n/a.	12	n/a	n/a	n/a n/a	The patient presented with transient gestational hyperthyroidism, vomiting, dehydration, confusion, abnormal behavior, hypomagnesemia (0.68 mmol/L), hypokalemia (3.3 mmol/L) and a 4-week history of vomiting. She had followed a liquid diet for the previous month due to severe vomiting. She was hospitalized for 14 days. She delivered vaginally at term. Birth weight was n/a.
#5. Damaso 2020 Brazil [23]	25-year-old G3P2	13 5/7	n/a	n/a	n/a n/a	The patient presented with weakness, emesis of 1-month, mental confusion, visual and auditory hallucinations, hypokalemia (3.3 mmol/L) and hypomagnesemia (1.4 mg/dL). Pregnancy outcome n/a.
#6. Tong 2020 India [24]	34-year-old G4P3	17	n/a	n/a	n/a n/a	The patient presented with dehydration, ataxia, 3 weeks of abnormal behavior, hypokalemia (3.0 mmol/L) , visual hallucinations, hyperparathyroidism, with an inability to take oral medication. She had been hospitalized 8 weeks earlier with over 10 emetic event per day. At discharge, the patient still had residual giddiness. Pregnancy outcome n/a.
#7. Dasari 2020 India [25]	Teen G1P0	13	n/a	n/a	n/a n/a	The patient's emesis started at 8 weeks gestation. At her admission, she presented with an inability to walk. Sodium reported @ 135 mEq/L and potassium @ 3.35 mEq/L. She was treated and discharged. She was induced at term for oligohydramnios and delivered a SGA 2.5 kg. male neonate. (AGA male neonate at 40 weeks is expected to weigh 2.9-3.4 kg.)
#8. Meggs 2020 USA [26]	27-year-old G1P0	17	n/a	n/a	n/a n/a	The patient presented with gallbladder sludge in addition to nausea, vomiting, and pain. She was treated and discharged. She was re-admitted 3 days later with altered mental status, deliria, with thiamin below the level of detectability. Level n/a. An ultra-sound revealed an IUFD for which the patient underwent a D&C. The hospital course was complicated by hypercalcemia (value n/a) secondary to hyperparathyroidism which was resected, an upper extremity venous thrombosis. Discharge to skilled nursing facility was recommended however her family elected home discharge with a home health aide.
#9. Shah 2020 USA [27]	18-year-old G1P0	18	n/a	166 lbs. (#)	n/a -18% loss/ -30 lbs.	The patient presented with vomiting, weight loss, a 5-day history of vertigo and hypokalemia (2.5 mmol/L) She had previously been on home IV hydration. On HD 2 the patient experienced an IUFD.
#10. Zigrai 2020 Slovenia [28]	35-year-old G2P1	9	n/a	n/a	n/a n/a	The patient presented to a local facility with persistent nausea and vomiting for 2 weeks and an inability to eat normally. When her condition deteriorated she was transferred to the reporting facility with muscle wasting, hypokalemia (2.63 mmol/L), hyponatremia (127 mmol/L). Treatment ensued with IM thiamin and parenteral supplementation with amino acids and glucose, with improvement in her condition. At 35 weeks, she delivered neonate with a cleft upper lip. At 7 months postpartum, an MRI scan of the patient's brain showed resolution of earlier deficits.

#11. Kirty 2021 India [29]	26-year-old G1P0	20	n/a	n/a	n/a n/a	The patient presented with gradually worsening quadriparesis of 2 weeks, dehydration, hyponatremia (126 mmol/L), hypokalemia (3.4 mEq/L) altered mental status and irrelevant talk. The patient's emesis began at 1-month gestation with treatment at various secondary care centers. After 3 weeks of treatment, her ophthalmoplegia began to resolve. At term, the patient delivered 2.2 kg. SGA male neonate. (AGA male neonate expected to weigh between 2.9-3.4 kg. at 40 weeks.) The patient continued with both short- and long-term memory issues postpartum.
#12. Ghosh 2021 India [30]	20-year-old G2P0	16	n/a	n/a	n/a n/a	The patient presented with recurrent convulsions, ataxia of 1 month, altered sensorium for 1 day and hyponatremia (130 mEq/L). Her uncontrollable nausea, vomiting and weight loss starting at week 4. Her thiamin at 2.84 mmol/L (range 70-180 mmol/L). Her medical history indicated a previous pregnancy with excessive vomiting and a mid-trimester fetal loss. By HD 14 patient was able to walk with support. The pregnancy was continued.
#13. Pagaling 2021 Philippines [31]	36-year-old G/P n/a	13	n/a	n/a	n/a n/a	The patient first presented at 6 weeks with intractable vomiting and generalized weakness. At the second admission the patient presented with double vision, a sodium reported as normal, vomiting and she eventually became comatose. Patient was aroused after 1 week of IV thiamin but continued with disorientation and amnesia. She experienced early preterm labor and a cesarean delivery was performed at 37 weeks. Postpartum she continued with persistent cognitive deficits, confabulation, and remained bedridden. The patient, wheel-chair dependent, was transferred to a rehabilitation facility.
#14. Divya 1 2021 India [32]	20-year-old G1P0	19	n/a	n/a	n/a n/a	The patient presented with 2-weeks of vomiting, dehydration, anemia, slurred speech, difficulty walking with hypomagnesemia (1.2 mg/dL). She was treated and hospitalized for 11 days. Fetal outcome n/a.
#15. Divya 2 2021 India [32]	29-year-old G5P113	17	n/a	n/a	n/a n/a	The patient presented with 2 weeks of vomiting, headache, dehydration, abnormal liver function tests, vision difficulties of 4 days' duration and was hospitalized 15 days. She delivered at 38 weeks a 2.2 kg. SGA female. (The AGA female at 38 weeks weighs approximately 2.8 kg.)
#16. Divya 3 2021 India [32]	38-year-old G2P1	20	n/a	n/a	n/a n/a	The patient presented with vomiting of 1 month, nystagmus, ataxia, drowsiness, hypokalemia (2.8 mEq/L) and treated with parenteral thiamin for 12 days. An antenatal scan revealed a missed abortion, and a 300-gram fetus was expelled. The patient was hospitalized for 14 days. (An AGA fetus at 21 weeks is expected to be weigh approximately 342 grams.)
#17. Divya 4 2021 India [32]	22-year-old G1P0	16	n/a	n/a	n/a n/a	The patient presented with weakness of 1-month, slurred speech of 5 days, and dehydration. At discharge she continued with paraparesis. The patiennt re-presented at 30 weeks with premature rupture of the membranes (PROM), delivering a SGA 1.3 kg. neonate who succumbed to prematurity DOL 20. (An AGA fetus at 30 weeks is expected to weigh approximately 1.4 kg.)
#18. Divya 5 2021 India [32]	25-year-old G1P0	19	n/a	n/a	n/a n/a	The patient presented with 2 months of daily emesis, ataxia, hypokalemia (2.5 mEq/L), 2 episodes of seizures in the prior week and elevated liver function tests. She continued with ataxia at discharge after a 28-day hospitalization. At 39 weeks, the patient delivered a SGA 2.5 kg. male neonate. (The AGA male neonate at 39 weeks is expected to weigh between 2.9-to 3.4 kg.)
#19. Divya 6 2021 India [32]	26-year-old G1P1	13 3/7	n/a	n/a	n/a n/a	The patient presented with emesis of 2 months, slurred speech, anemia, aggressive behavior of 3 days and hypokalemia (value n/a) and had a 12 day hospitalization. Pregnancy outcome n/a.
#20. Jdidia 2021 Tunisia [33]	33-year-old G2P1	15	n/a	n/a	n/a n/a	The patient presented with weakness, amnesia, confusion, paresthesia, and hypokalemia (2.4 mmol/L). A bilateral ophthalmoscopy revealed a superficial retinal hemorrhage. She had previously presented to outside provider 25 days earlier with excessive nausea and vomiting and was prescribed anti-emetics. The patient was able to walk with assistance at discharge. Pregnancy outcome n/a.
#21. Llansó 2022 Spain [34]	33-year-old G2P1 Japanese	13	n/a	n/a	n/a n/a	The patient presented with vomiting, low-grade fever, evidence of renal failure, abnormal LFT, and hypokalemia (n/a). At 24 weeks' the patient was still experiencing mild gait instability and antegrade memory loss. Her medical history included a history of HG in a previous pregnancy. Pregnancy outcome n/a.

#22. Mehreen 2022 Pakistan [35]	35-year-old G12P1SA10	19	n/a	n/a	n/a n/a	The patient had a history of 10 unexplained pregnancy losses and presented with intractable vomiting since early gestation, diet controlled gestational diabetes, A1c 6.1%, hypokalemia (2.8 mmol/L) and hypomagnesemia (1.66 mg/dL). On admission she had hyperglycemia (n/a). On HD 2 the patient developed severe abdominal pain due to gallbladder sludge and single calculus which was removed laparoscopically but became severely acidotic being transferred to an ICU and intubated with DKA. Cultures returned positive for Acinetobacter. The DKA resolved HD 3 and cerclage was placed for an opened cervix. Unfortunately, the patient experienced an IUFD. Fetal weight n/a. A two-month hospitalization followed.
#23. Punal 2022 USA [36]	19-year-old G2P1	17	n/a	n/a	n/a -13.6 kg./-30 lbs. weight loss	The patient presented with AMS from an abortion service with dehydration, hypokalemia (2.7 mmol/L) and hyponatremia (132 mmol/L) with two previous presentations to an OSH with severe vomiting and severe electrolyte abnormalities. She was treated and discharged on HD 23 with a walker, deciding to continue the pregnancy.
#24. Rane 1 2022 India [37]	Age n/a G/P: n/a	15	n/a	BMI 21 kg/m2	n/a -14 kg./ -30.8 lbs. loss	The patient presented at 15 weeks, with 6 weeks of emesis, memory loss, nystagmus, confusion, ataxia, hyponatremia (133 mEq/L) and hypokalemia (3.1 mEq/L). Pregnancy outcome n/a.
#25. Rane 2 2022 India [37]	Age n/a G/P: n/a	15	n/a	BMI 26	n/a -9 kg./ -19.8 lbs. loss	The patient presented at 15 weeks with emesis of 5 weeks, memory loss, double vision, delirium, confusion, ataxia, hyponatremia (131 mEq/L) and hypokalemia (3.1 mEq/L). Pregnancy outcome n/a.
#26. Rane 3 2022 India [37]	Age n/a G/P: n/a	25	n/a	BMI 28	n/a -11 kg. /-24.2 lbs. loss	The patient presented at 25 weeks with emesis of 9 weeks, double vision, ataxia, and normal serum sodium (n/a) and potassium levels (n/a). Pregnancy outcome n/a.
#27. Rane 4 2022 India [37]	Age n/a G/P: n/a	19	n/a	BMI 23	n/a -12 kg./ -26.4 lbs. loss	The patient presented at 19 weeks with emesis of 4 weeks, memory loss, confusion, confabulation, hyponatremia (130 mEq/L) and hypokalemia (2.3 mEq/L). Pregnancy outcome n/a.
#28. Rane 5 2022 India [37]	Age n/a G/P: n/a	19	n/a	BMI 19	n/a -1 kg./ --2.2 lbs. loss	The patient presented at 17 weeks with emesis of 5 weeks, nystagmus, ataxia, hyponatremia (132 mEq/L), and hypokalemia (3.3 mEq/L). Pregnancy outcome n/a.
#29 . Ramratten 2022 Spain [38]	36-year-old G4P3	30 1/7 (30 weeks 1 day)	n/a	n/a	n/a. -18.1 kg. / -40 lbs. loss	The patient presented with transaminitis, low platelets, rhabdomyolysis, hypophosphatemia (2.25 mg/dL), hypernatremia (138 mmol/L), hypokalemia (1.8 mmol/L), magnesium at 1.87 mg/dL and calcium at 8.7 mg/dL. Her emesis commenced in the first trimester. A naso-jejunal feeding tube was placed and refeeding syndrome (RFS) occurred with phosphorus dropping to 1.8 mmol/L necessitating feeding titration to 430 calories/day on HD 4. Phosphorus plummeted further to 0.4 mg/dL. IV phosphorus was unavailable, requiring phosphorus repletion via N-J enteral tube. Multi-disciplinary team conferences with the expertise of a dietitian for nutrition management occurred. The patient experienced a 3-week hospitalization. Pregnancy outcome n/a.
#30. Barcenta Casadesus 2022 USA [39]	Early 20's G3P1011	15	n/a	n/a	n/a n/a	The patient was previously seen at 6 weeks at an OSH, diagnosed with pancreatitis and hepatitis A. She re-presented at 15 weeks with confusion, altered mental status, weakness, ataxia, nausea, and vomiting, elevated LFT and lipase. Labs n/a. Discharged to acute rehab. Pregnancy outcome n/a.
#31. Kumar 2022 India [40]	22-year-old G/P: n/a	28	n/a	n/a	n/a n/a	The patient presented with confusion, vision loss due to retinal hemorrhages, bilateral papilledema, hyponatremia (128 mEq/dL), and hypokalemia (2.9 mEq/dL). Pregnancy outcome n/a.
#32. Olmsted 2023 USA [41]	33-year-old African-American G1P0	15	n/a	n/a	n/a n/a	The patient was transferred to the tertiary care facility after 10-day hospitalization at local facility with severe HG, transaminitis and auditory hallucinations, elevated LFT's, hypernatremia (147 mmol/L), hypokalemia (2.8 mmol/L), hypomagnesemia (1.4 mg/dL), and rhabdomyolysis. On HD 18 the patient experienced an IUFD. EFW n/a. A 47-day hospitalization followed.
#33. Banumathi 2023 India [42]	19 yr-old G1P0	16	n/a	60 kg.	45 kg. -15 kg. (-25%)	The patient presented at 16 weeks with complaints of swaying when walking, abnormal eye movements and difficulty reading for previous two days with multiple first trimester admissions to a general hospital earlier in the pregnancy. Her fundus optic disc was found to be hyperemic with mild edema, peripapillary hemorrhages, tortuous veins and with severe ataxia on standing and walking. An abdominal ultrasound revealed markedly distended gall bladder with calculi and echogenic sludge which was treated. Electrolytes reported as corrected (n/a). After 1 week of treatment, the patient was able to ambulate normally. Pregnancy outcome n/a.

#34. Ben Chaib 2023 Morocco [43]	25 yr-old G1P0	17	n/a	59 kg.	n/a n/a	Initially, the patient presented at 17 weeks with persistent vomiting and general weakness beginning at week 8 of gestation. At 17 weeks, she complained of tetraparesis and presented to the emergency department and was treated with IV fluids, dextrose, anti-emetics and referred to the ICU with a potassium of 2.8 mEq/L. Level of thiamin was 10 nmol/L (NR: 74-222 nmol). The potassium was repleted but with no improvement clinically. Antiemetics were able to controlled the emesis. On HD 19 her condition improved and she was able to walk, being discharged home on HD 37 with mild ataxia. Pregnancy outcome n/a.
#35. Fiorenti 2023 Italy [44]	27 year-old G1P0	13	n/a	n/a	n/a	The patient presented for care at 8 weeks gestation with persistent NVP of 2 weeks duration, was treated with antiemetics and discharged. She then re-presented at 13 weeks to Emergency with intense asthenia, nausea, mental confusion and was admitted. MRI showed FLAIR sequence in anterior portion of the third ventricle. The hospitalization was complicated by gestational hypertension and hypercalcemia (n/a) being diagnosed with atypical parathyroid adenoma. She was diagnosed with persistent malnutrition with initiation of parenteral nutrition and discharged to a rehabilitation facility. Representation occurred at 23 weeks gestation with positive blood cultures for Staphylococcus aureus MRSA and the need for IV antibiotics. Doppler ultrasound performed at the level of the midline catheter showed thrombus extending to axillary and subclavian veins. Anticoagulation therapy was implemented. She re-presented at 33 weeks with preterm labor. At 38 weeks she was delivered of a 3070 g female neonate via cesarean section. (The average 38-week female weight is expected to weigh 3.25 kg.) One month postpartum, the patient was able to walk normally but still experienced nystagmus, weak reflexes with both short- and long-term memory impairment.
#36 Alaithan 2023 Saudi [45]	23-year-old Sudanese G1P0	17	n/a	n/a	n/a	The patient presented to emergency with dizziness, lower leg weakness, visual and auditory hallucinations, hypokalemia (2.9 mEq/L), hypophosphatemia (0.54 mmol/L) and hypocalcemia (2.80 mg/dL) with a 3 month history of persistent emesis She was found to have altered level of consciousness, GCS of 13/15, hypokalemia-induced periodical paralysis, treated for 10 days and discharged. Pregnancy outcome was n/a. Pregnancy outcome n/a.
#37 Borgemenke 2023 India [46]	22-year-old G1P0	13	n/a	n/a	n/a -30 lbs./-13.6 kg.	The patient presented with altered mental status, blurred vision, and dizziness. Her medical history included asthmas and polycystic ovarian syndrome with hyponatremia (133 mmol/L), elevated liver functions but a negative hepatitis panel. Prior to the current presentation, the patient was hospitalized for 5 days with HG. Found also to have a low folate (3.28 ng/mL) which was addressed. Nutrition was consulted along with neurology but details n/a. One year after initial presentation, a repeat brain MRI demonstrated complete resolution. Outcome of pregnancy n/a.
#38 Ye 2023 India [47]	33-year-old G: n/a P: n/a	16	n/a	n/a	n/a -13 kg./-28.6 lbs.	The patient presented with general weakness, blurred vision of 3 weeks and an inability to stand or walk for 1.5 weeks. The HG onset occurred in the early first trimester with a rapid weight loss of 3 months. Her past medical history included hypothyroidism since age 13 which was being treated. Imaging of both eyes confirmed presence of peri-aphillary sub-retinal exudates and bilateral hemorrhages. Treatment included IV fluids, vitamins, and other supportive treatment (n/a). After two weeks of care, patient experienced a complete resolution and delivered a healthy infant at term. (Details n/a).
#39 Gonzalez 2023 Country not provided due to concerns for privacy. [48]	29 year-old West African G: n/a P: n/a	21	n/a	n/a	n/a	The patient presented with altered mental status, decreased verbal output, agitation, and ataxia. Attempts at re-evaluation were limited by medical complications and prolonged hospitalization. Details n/a. Repeat in-patient evaluations 5 months following the birth of a healthy child demonstrated profound memory impairment but improved cognitive capacity and engagement.

All gravidas were treated with various doses of thiamin and medications.

The author acknowledges that the measurement units of electrolytes differ by country: mg/dL, mmol/L, and mEq/L.

Abbreviations: AMS: altered mental status. HD = hospital day. AGA = average for gestational age. SGA = small for gestational age. N/a = not available. EFW: estimated fetal weight. MRI: magnetic resonance imaging. IUFD: intrauterine fetal demise.

The resulting malnutrition to the fetus can manifest in growth restriction, vitamin K embryopathy, premature delivery, intra-uterine fetal demise (IUFD) and impaired cognitive development [67-72]. Women with poorly managed HG and WE have a high rate of fetal demise approaching 50% [12].

We observed a gross lack of anthropometric data in these reports regarding nutritional status. There were 3 indications nutrition support was provided; two as intravenous amino acids, glucose and supplemental nutrients; one with complications of sepsis, occurring at the rehabilitation facility [44]. A third gravida was provided a naso-jejunal enteral feeding which was complicated by refeeding syndrome (RFS) which can occur when a starved individual is provided aggressive nutrition, depleting electrolytes as new cells are being created, causing major organ dysfunction [38]. The Zigrai report lacked specifics regarding the amount and rate of amino acid and glucose infusion, placement of the catheter and duration of therapy [28]. The Florenti report et al. also lacked specifics of solution composition and electrolyte status. In the Ramratten report, which included a dietitian, nutrition was provided via naso-jejunal feeding tube, however there were no details of goal caloric and protein requirements, the enteral product selected, duration of therapy, and neonatal outcome [38].

While 11 of the 39 reports (28%) included weight loss, there was no discussion of the expected gains recommended by the National Academy of Sciences (NAS) and IOM in 2009 by gestational age [73]. In these 11 cases, the gross weight losses ranged from -1 kg./-2.2 lbs. to -18.1 kg./ -40.0 lbs. a total of 131 kg./289 lbs. or an average of 11.9 kg./26 lbs. per gravida. In the review by Oudman et al. the fetal loss of HG-WE pregnancies was 50%, with an average maternal weight loss of -12.1 kg./-26.2 lbs. with illness averaging 7 weeks [16]. Table 2, Net weight loss by gestational age compared to recommended gains by IOM, provides our interpretation of weight loss in pregnancy, by adding the expected lack of gain to the cited loss if it was provided in the report.

Data tabulated in the Net weight loss column illustrate the magnitude of the caloric deficit, which is 131 kg./239 lbs. or 11.9 kg./26 lbs. loss per gravida. Assuming 3500 calories per pound of weight, this equates to negative 102,900 calories per pregnant woman.

Figure 1 illustrates gestational weight recommendations with advancing weeks of gestation.
The solid line at the bottom of the graphic starting at "zero" on the horizontal axis represents a woman's pre-gravid weight. Weights below this line during pregnancy indicate a negative gain, a state of catabolism. IOM has never advocated weight loss in pregnancy. Weight gain has been recommended by the US NAS/IOM by BMI and gestational age to optimize pregnancy outcome, preventing small-for-gestational age infants and preterm births.

Inadequate nutrition also fails to deliver required electrolytes to maintain maternal cognitive and vital organ function. Vital organs are sustained by adequate nutrition which includes energy, protein, essential fatty acids, vitamins, and minerals and are compromised in the catabolic setting of severe and unintended weight loss. The human brain requires 28% of daily maintenance energy intake for adequate cognitive functioning which is approximately 450-500 calories.

Table 2: Net weight loss by gestational age compared to IOM recommended gains.

Patient #/ Reference/ country	Gestational Age (in weeks) at presentation.	Actual weight loss in pregnancy (kg./lbs.)	Expected minimum gain per IOM (kg./ lbs.) (See Figure 1 below)	Net weight loss: Documented loss PLUS lack of gain. (kg./lbs.)
# 9 Shah USA [27]	18	-13.6 kg./-30 lbs.	1.36 kg./3 lbs.	-15 kg./-33 lbs.
# 23 Punal India [36]	17	-13.6 kg./-30 lbs.	0.9 kg../2 lbs.	-14.5 kg./-32 lbs.
# 24 Rane 1 India [37]	15	-14 kg./-30.8 lbs.	0.9 kg/2.0 lbs	-14.9 kg./-32.8 lbs.
# 25 Rane 2 India [37]	15	-9 kg./-19.8 lbs.	0.9 kg./2.0 lbs.	-9.9 kg./-21.8 lbs.
# 26 Rane 3 India [37]	25	-11 kg./-24.2 lbs.	2.27kg./5 lbs.	-13.3 kg./-29.2 lbs.
# 27 Rane 4 India [37]	19	-12 kg./-20.4 lbs.	1.8 kg./4 lbs.	-13.8 kg./-30.4 lbs.
# 28 Rane 5 India [37]	19	-1 kg./-2.2 lbs.	1.8 kg./4 lbs.	-2.8 kg./-6.2 lbs.
# 29 Ramratten Spain [38]	30 1/7	-18.1 kg./-40 lbs.	4.5 kg./8 lbs.	-22.6 kg./-50 lbs.
#33 Banumathi India [42]	16	-15 kg./-33 lbs.	1.3 kg./2.8 lbs.	-16.3 kg./-36 lbs.
#37 Borgemenke India [46]	13	-13.63 kg./-30 lbs.	0.45 kg./1.0 lbs.	-14.0 kg./-30.7 lbs.
#38 Ye India [47]	16	-13 kg./-28.7 lbs.	0.9 kg./2.0 lbs.	-13.9 kg./30.7 lbs.
11 women		Gross total weight loss: 131 kg./290 lbs.	Per gravida: 11.9 kg./26 lbs.	

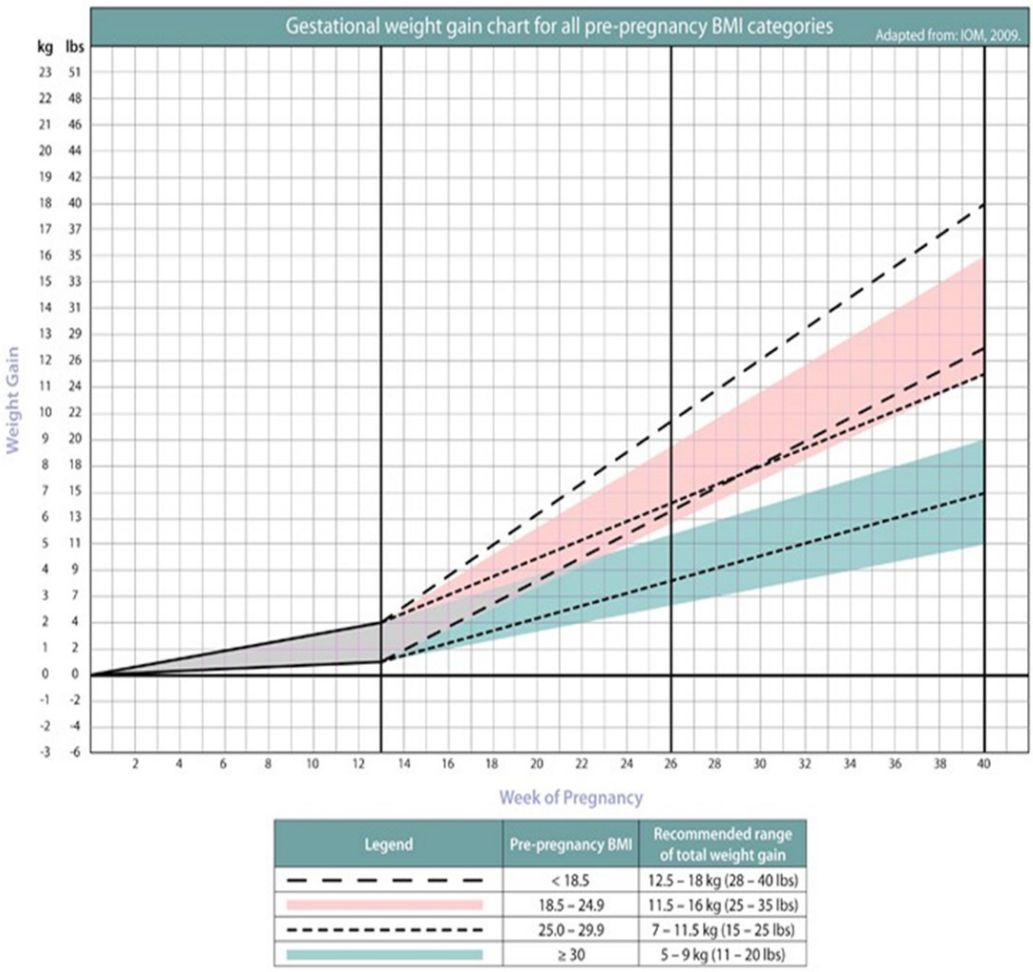

Figure 1: Weight gain by BMI and gestational age.

National Academy of Sciences, Institute of Medicine. Washington, DC. 2009 [73].

Oudman et al. noted cognitive dysfunction affected 65.4% of the women in their review; 37.4% experienced double vision and blurred vision affected 27.4% [12]. Sixteen women in our review (41%) presented with visual difficulties: (patients # 1,2, 3,11,13, 15,20, 24,25,26,28,31,32,33,37, and 38,) while one-third (14/39) of gravidas presented with hallucinations and/or altered mental status (AMS) at the time of being diagnosed with WE. These are patients # 3, 5, 8, 11, 12, 20, 24, 25, 27, 30, 32, 35, 37, and 39.

Table 3, Electrolyte status of 15 gravidas with HG who presented with cognitive dysfunction, provides a summary of abnormal electrolytes associated with hallucinations, AMS and/or confusion at admission.

Electrolytes affect cardiac contractility and exert neuro-muscular influence, which contributes to cognitive functioning [74-76]. Hallucinations can be precipitated by a number of factors including various medications, medical illnesses such as schizophrenia, Parkinson's and Alzheimer's, substance abuse, alcohol withdrawal, major medical conditions, trauma, dehydration, malnutrition, electrolyte anomalies notably magnesium, potassium, sodium, phosphorus and calcium, sleep deprivation, and pain [77-84].

Table 4, Problems associated with low electrolytes, provides a summary of electrolytes as related to cognitive, respiratory, cardiac functions and overall well-being [74-76].

Five patients, # 9,18,20,27,29, (13%) presented with severe hypokalemia, which can be associated with serious cardiac arrhythmias and sudden death [85-87].

Severe consequences have been reported with vitamin, mineral, and energy deficiencies [60-67,81-83,85-86,88-92]. Volumetric reductions in both the brain and heart have been documented in persons with eating disorders [91-92]. Researchers have demonstrated a loss of brain volume of 3.7% in adults and 7.6% loss in adolescents with anorexia nervosa as well as a 50% reduction in the left ventricular ejection function (LVEF) [92]. In severe maternal starvation/malnutrition, it would be reasonable to consider the vital organs of the fetus might be compromised similarly. Pregnancy is comprised of more than a developing fetus. The ancillary components of pregnancy are depicted in Table 5, Components of pregnancy (or the products of conception (POC) [93].

Table 3: Electrolyte status of 15 gravidas with HG who presented with cognitive dysfunction.

Patient #/ GA wks. Reference #/ Year country	Type of cognitive dysfunction: Hallucination/ AMS/deliria/ confusion/	Na+	K+	P04	Mg++	Ca++	Wt. loss	Wks. Of illness	Comments
#3 19 wks. Mishra [21] 2019 India	Visual and auditory hallucinations. Confusion. Diagnosed with Korsakoff psychosis	n/a	n/a	n/a	n/a	n/a	n/a	>11	Electrolytes reported as normal.
#5 13 5/7 wks. Damaso [23] 2020 India	Visual and auditory hallucination	n/a	3.3	n/a	1.4	n/a	n/a	~4	
#8 17 wks. Meggs [26] 2020 USA	AMS, deliria	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Thiamin reported below detectable level. (n/a) IUFD @ 17 3/7 weeks
#11 20 wks. Kirty [29] 2021 India	AMS	126	3.4	n/a	n/a	n/a	n/a	>12	
#12 16 wks. Ghosh [30] 2021 India	AMS	130	n/a	n/a	n/a	n/a	n/a	~12	Thiamin at 2.84 mmol/L (ref: 70-180 mmol/L)
#20 15 wks. Jdidia [33] 2021 Tunisia	Confusion	n/a	2.4	n/a	n/a	n/a	n/a	~ 3	Ophthalmo-scopy showed bilateral superficial retinal hemor-rhages.
#24 15 wks. Rane 1 [37] 2022 India	Confusion	133	3.1	n/a	n/a	n/a	-14 kg.	6	
#25 15 wks. Rane 2 [37] 2022 India	Deliria, confusion	131	n/a	n/a	n/a	n/a	9 kg.	5	
#27 19 wks. Rane 4 [37] 2022 India	Confusion	130	2.3	n/a	n/a	n/a	12 kg.	>5	
#30 15 wks. Casadesus [39] 2022 USA	AMS, confusion	n/a	n/a	n/a	n/a	n/a	n/a	9	First seen at OSH at 6 weeks. Diagnosed with pancreatitis and hepatitis A.

#31 28 weeks Kumar [40] 2022 India	Confusion	128	2.9	n/a	n/a	n/a	n/a	n/a	
#32 15 wks. Olmstead [41] 2023 USA	Auditory hallucinations	147	2.8	n/a	1.4	10.4	n/a	~2	IUFD ~ 17 4/7 weeks
#35 13 weeks Fiorentini [44] 2023 Italy	Confusion	n/a	n/a	n/a	n/a	n/a	n/a	~ 11	Started on PN ~ 13 weeks. (Details lacking)
#37 13 weeks Borgemenke [46] 2023 India	AMS	132	n/a	Po4	mg	n/a	-13.16 kg./ -30 lbs.		
#39 16 weeks. Gonzales [48] 2023 N/A	AMS	n/a	n/a	n/a	n/a	n/a	n/a		

Na+ = sodium (mmol/L) K+ = potassium (mmol/L) Mg++ = magnesium (mg/dL) P04 = phosphorus (mg/dL) Ca++ = calcium (mg/dL)

Table 4: Problems associated with low electrolytes.

Electrolyte	Symptoms	Ranges
Sodium (Na+)	Anorexia, nausea, vomiting, lethargy, confusion, muscle twitching, coma, seizures.	Reference range: 135-145 mEq/L 120-125 mEq/L: mild 115-120 mEq/L: moderate <110-115 mEq/L: severe (permanent neurological damage at extremely low levels)
Potassium (K+)	Fatigue, weakness, cramps, rhabdomyolysis, cardiac dysfunctions, ST -segment depression, flattened T waves, ventricular, presence of U wave, ventricular dysrhythmias, tachycardia, decreased bowel motility/ileus.	Reference range: 3.5-5.0 mEq/L 3.0-3.5 mEq/L: mild 2.5-3.0 mEq/L: moderate <2.5 mEq/L: severe Hypomagnesemia may contribute to the development of hypokalemia. Severe hypokalemia may cause dysrhythmias, hypoventilation, paralysis, and decreased cardiac output related to altered conduction.
Magnesium (Mg++)	Muscle weakness, muscle twitching, cramps, parathesis, arrhythmias, ECG changes, depression, agitation, confusion, psychosis.	Range 1.8-3.0 mg/dL Deficiency: <1.8 mg/dL. Required in thiamin metabolism.
Calcium (Ca++)	Numbness, tingling of fingers, muscle cramps, convulsions, decreased myocardial contractility, ECG changes, prolonged QT interval caused by, elongation of ST segment, may develop a form of ventricular tachycardia called torsades de pointes. Also manifests as emotional instability, anxiety, or frank psychosis.	Range: 8.5-10.5 mg/dL Deficiency: <8.5 mg/dL The body maintains a tight range of calcium.
Phosphorus (P04)	Paresthesias, muscle weakness, muscle pain, mental changes, acute respiratory failure, decreased cardiac contractility and tissue oxygenation, seizures. Phosphorus is a component of 2,3-diphosphoglycerate (DPG) which facilitates oxygen delivery to the tissues.	Reference: 2.5-4.5 mg/dL <2.5 mg/dL = severe <1 mg/dL may be potentially lethal because of altered cellular function, which includes decreased myocardial function, and increased pulmonary artery wedge pressure (PAWP). Phosphorus is required in thiamin metabolism.

Table 5: Components of pregnancy (or the products of conception) at term, 40 weeks.

Component	Weight in pounds and kg.	Percentage of total weight
Fetus	7.5*-8.5 [3.4-3.86]	27.2*
Placenta and umbilical cord	1.5 [0.68]	5.4
Amniotic fluid volume	1.8 [0.818]	6.5
Tissue fluids	2.7 [1.23]	9.8
Uterus	2.0 [0.909]	7.3
Maternal protein and adipose stores	7.5 [3.409]	27.2
Breast tissue	1.0 [0.45]	3.6
Blood	4.0 [1.818]	14.5
	27.5* [12.5]	~100.0

In 11 cases in this review where weight information was provided, the weight loss mid gestation exceeded the suggested total gain for the entire pregnancy, which was over 13.6 kg/30 lbs. These were patients # 9, 23, 24, 25,26,27,28, 29, 33,37and 38.

Severe maternal dehydration decreases amniotic fluid volume (AFV) [94]. Six pregnant ewes which were water-deprived for 54 hours demonstrated an AFV reduction of 35%; from 871 +/- 106 ml to 520 +/-107 ml [95]. Oligohydramnios, defined as AFV less than expected for gestational age, results in fetal deformations due to constricted uterine space, umbilical cord compression and death [96]. Dehydration reduces the capacity to maintain adequate maternal intravascular blood volume and placental blood flow impacting nutrient, energy and oxygen delivery to the fetus and placenta [97]. Cord compression also decreases oxygen, energy and various nutrients to support growth and development of major organs, including the brain, heart, lung, kidneys and liver of the developing fetus [98-100]. None of the reports in our review commented on AFV.

In our review, which included 39 women and 41 fetuses, there were 5 IUFDs and 4 neonatal demises. One neonate born at 30 weeks' gestation succumbed to prematurity on day of life 20 and a set of prematurely born triplets at 24.5 weeks died shortly after delivery for a pregnancy wastage rate of 22 %. Details of the 5 fetuses who suffered intra-uterine deaths are detailed in Table 6.

In 3 cases of the 5 IUFD, low maternal electrolytes and prolonged poor nutrition were evident. We also noted 7 SGA neonates and 2 preterm births. It is highly possible the IUFD described by Shah et al. may have experienced a fatal cardiac arrhythmia as the patient admitted with severe hypokalemia at 2.5 mmol/L. and a weight loss of 18% [27]. Patient #16 described by Divya et al. experienced a missed abortion at 20 weeks was hypokalemic (2.8 mEq/L) on admission, as was patient #32 described by Olmsted et al. who suffered an IUFD at 15 weeks with an admission potassium of 2.8 mmol/L [27,36].

We also searched PubMed for reports of HG and fetal loss to evaluate electrolytes and weight loss and found two cases. Walsh et al. described a 39-year-old G8P6 Pacific Islander woman with pre-gravid BMI 36, who presented at 15.5 weeks with an out-of-hospital cardiac arrest and hypokalemia at 2.1 mmol/L due to severe HG [64]. On admission, the patient was acidotic with a pH of 6.7, hypokalemic at 2.1 mmol/L. with a weight loss of 9.0% of her pre-gravid weight. On HD 2, the patient suffered a fetal demise. These data suggest hypokalemia may have a contributing role in

Table 6: Clinical data on cases of IUFD (intra uterine fetal demises).

Patient #/ Reference #/ Country	Gestational age (in weeks) at admission	Weeks of illness	Maternal Weight loss	Maternal electrolyte status on admission.	Hospital Day of IUFD
# 8 Meggs (26) USA	17	n/a	n/a	n/a	~ 1
# 9 Shah (27) USA	18	n/a	-13.6 kg./-30 lbs.	Hypokalemia (2.5 mmol/L.)	2
# 16 Divya 3 (32) India	20	At least 4 weeks	n/a	Hypokalemia (2.8 mmol/L.	5
# 22 Mehreen (35) Pakistan	19	Since early gestation	n/a	Hypokalemia (2.8 mmol/L.), hypomagnesemia (1.66 mg/dL.), hyperglycemia (n/a). A1c 6.1%. On HD 3 the patient developed a severe metabolic acidosis with pH 6.8, was septic and transferred to an ICU in DKA, which resolved. A cerclage was placed for an open internal OS after patient was stabilized. Patient subsequently experienced an IUFD. Tracheal cultures were positive for MRSA which was treated.	5
# 32 Olmsted (41) USA	15	n/a	n/a	Hypernatremia (147 mmol/L.), hypokalemia (2.8 mmol/L.), hypomagnesemia @ 1.4 mg/dL. Phosphorus n/a. Hypercalcemia @ 10.4 mg/dL	18

this IUFD but a complicating element was maternal acidosis and a 10 kg./ 22 lbs. weight loss. The patient's expected 15.5-week minimum weight gain was 1 kg./2 lbs. The lack of expected weight gain added to the 10 kg. weight loss brings the negative gestational weight loss to 11 kg./ 24.2 lbs.

Mayer and McGill described a fetal loss experienced by a 32-year-old gravida, G5P4, who presented at 16 weeks with a 13.6 kg./30 lbs. weight loss in 6 weeks, hyponatremia (131 mg/dL), hypomagnesemia (2.3 mg/dL), hypokalemia (2.3 mmol/L), and hypophosphatemia (1.6 mg/dL) [101]. On HD 2 at 3AM the patient was provided 1 L of dextrose normal saline solution with added magnesium, folic acid, thiamin, and anti-emetics prior to a scheduled fetal ultra-sound. At 7AM the patient experienced reduced nausea and expressed a desire to eat breakfast. Dextrose IV fluids were started simultaneously as the fetal assessment was scheduled. Maternal phosphorus plummeted to 1.5 mg/dL after the IV solution was started as the serum lipase doubled to 1060 units/L. Fetal activity was absent. Hypophosphatemia continued (1.4 mg/dL) while lipase remained elevated at 1083 units/L on HD 3, then both decreased. A female fetus weighing 102 g. was expelled. The patient was subsequently diagnosed with RFS by medical consultation. A 33-day hospitalization ensued, and the patient was eventually discharged with short term memory impairment. Neither of these two patients of Mayer and McGill or Walsh were diagnosed with WE. The latter fetal demise suggests a contributing role of abnormally low sodium, magnesium, potassium and phosphorus, however the 13.6 kg./ 30 lbs. weight loss in six weeks is considered severe. At 16 weeks the expected weight gain, in a high BMI gravida of 36, would be 1 kg./2 lbs. Adding the weight loss of 13.6 kg. /30 lbs. to an expected gain of 1 kg. produces a net weight loss of 14.6 kg./ 32 lbs. and indicates a catabolic gestation. As noted by Oudman et al., fetal loss approaches 50% with a 12.2 kg. maternal weight loss, which both women experienced [12].

As electrolyte status impacts maternal cardiac status, there is a possibility the fetus may respond similarly. Anderson and Hansen reported a case of chronic fetal bradycardia (<120 bpm) in a 26-year-old primigravida seen at 38 weeks of gestation with blood pressures of 150/92 and provided one dose of Diupress (a diuretic) per day [102]. The patient returned one week later with normal blood pressures and hypokalemia at 3.3 mmol/L. The fetal heart rate (FHR) was bradycardic at 65-70 bpm. The patient was provided an infusion of dilute potassium chloride (30 mEq) over 1.5 hours with occasional frequent bursts of FHR to the 130-bpm range. The FHR normalized and the patient was discharged the following day. This report suggests that maternal hypokalemia at 3.3 mmol/L resulted in fetal bradycardia however the status of other electrolytes was not provided.

Murlitharan et al. described a 29-year-old G2P1 L1 gravida who presented at 18 weeks with 12-15 episodes of emesis per day for 14 days, moderate anemia (hemoglobin at 6 g/dL) of normocytic normochromic type, hyponatremia (106 mg/dL), hypokalemia (2.7 mg/dL), hypochloremia (93 mg/dL), hypocalcemia (8.3 mg/dL), hypomagnesemia (1.5 mg/dL), and hypophosphatemia (2.9 mg/dL) [103]. Vitamin D was low at 15 ng/ml with a normal parathyroid hormone (PTH) level. Arterial blood gas analysis was reported as normal. Maternal electrocardiogram (ECG) showed a prolonged QT interval (corrected QT interval of 536 m sec) and U waves. The patient's ECG normalized with the correction of electrolytes. This report points to the potential involvement of five major electrolytes—sodium, potassium, calcium, magnesium, and phosphorus in the maternal prolonged QT interval with U waves. The FHR and maternal weight were undisclosed.

Poor nutrition in pregnancy results in fetal growth compromise, more preterm births, a reduction in offspring IQ as well as increased rates of behavioral problems and autism [104,105]. The consequences of gestational malnutrition on the fetus/neonate/toddler/adolescent, and eventually the adult are life-long. In the Netherlands food deprivation in pregnancy due to Nazi blockades in WWII were traced to increased rates of adult schizophrenia [104,105]. Similarly, during China's "Great Leap forward" from 1959-1961 when agricultural land was reduced to increase manufacturing capabilities, followed by a massive famine which dramatically reduced food supplies, an estimated 25-30 million Chinese people died from starvation. Thirty to 35 million fewer births than might have been expected also resulted [106]. Among the pregnancies, which survived on a marginal diet, increased rates of schizophrenia in the offspring were found [107-110].

When protein intake is low, amino acids (AAs) essential for protein synthesis and other nitrogenous substances such as catecholamine's, creatine, dopamine, nitric oxide, polyamines, and thyroid hormones are limited. Low maternal dietary protein intake is linked to intrauterine growth restriction (IUGR). The placenta requires adequate levels of AAs for proper growth and development to supply nutrients to the fetus [111]. Amniotic fluid of a healthy pregnancy, which the developing fetus regularly swallows, contains varying levels of AAs and growth factors critical for fetal lung development and is reflective of the maternal diet [112].

Figure 2, Fetal development from conception to term, divides the embryonic and fetal periods. Vital organ development begins very early in conception, in the first half of the first trimester which is weeks 1-13. The second trimester extends from 14 to week 26 or 27 and the third trimester weeks 28 to term, approximately 40 weeks. Caloric needs in the normal healthy pregnancy do not generally increase until the second trimester begins, adding 340 calories additionally per day to the maternal diet. Fetal demands increase with an enlarging body and brain in the third trimester to an extra 452 calories per day in the gravida who begins pregnancy with a normal BMI. As the brain begins development very early, it is imperative that certain nutrients be in adequate supply at that time, such as folic acid (to prevent neural tube defects) and iodine (to prevent cretinism).

Ultrasound biometry has demonstrated fetal growth reduction precedes IUFD [114]. A smaller fetal liver contains reduced stores of glycogen. The IUGR fetus is also hypoglycemic with

reduced glycogen availability approximately 50% of the normal AGA fetus. A lower blood glucose level reduces oxygen uptake by the cerebrum [115,116]. A growth-restricted preterm infant is clinically at high risk for RFS as early as 24 hours after delivery which provides suspicion that the fetus of a chronically electrolyte depleted gravida is also at risk for RFS [117]. All 39 gravidas were identified with WE on admission. It is curious magnesium was reported in only 5 cases: patients # 4,5,22,29, and 32, while phosphorus was reported, monitored, and repleted in two instances: patients # 29 and 36. The etiology of WE is a deficiency of vitamin B1 or thiamin, yet only 3 cases had a thiamin level reported: patients # 8, 12, and 34**.** It is suspected that if maternal thiamin levels were depleted, the level in the fetus would likewise be affected. Thiamin deficiency has been speculated to be involved in sudden infant death syndrome or SIDS. The brainstem, cerebellum and limbic system of the brain are–highly sensitive to thiamin deficiency with the pathophysiology being similar to that of a continued state of a mild oxygen deprivation or pseudo-hypoxia. Dietary thiamin requires the cooperation of the SLC19 family of thiamin transporters for its absorption into cells and research shows that transporter SNPs (single nucleotide polymorphisms) may be relatively common and may increase genetic risk. Thiamin is dependent on magnesium as a co-factor for its role in metabolizing glucose in the energy generating processes of the pentose phosphate pathway and the Krebs cycle in the mitochondria of the cells [118]. Consequently, thiamin supplementation may be ineffective if existing or developing magnesium deficiency is not corrected simultaneously [59-60]. Thiamin is a co-factor in several key enzymes important in energy metabolism, including transketolase, alpha-ketoglutarate dehydrogenase, and pyruvate dehydrogenase. After absorption, dietary forms of thiamin enter cells via transport proteins. Once inside, free thiamin must be converted into thiamin pyrophosphate (TPP), the biochemically active coenzyme form. TPP is also referred to as thiamin diphosphate (TDP). This conversion, or phosphorylation, is achieved by an enzyme called thiamin pyrophosphokinase, which removes phosphate from adenosine triphosphate (ATP) and adds it to thiamin to make TPP. Concomitant electrolyte abnormalities, in the setting of magnesium deficiency, include hypokalemia and hypocalcemia, both of which are refractory to treatment until the magnesium deficiency is corrected. Magnesium deficiency has been implicated in precipitating WE [60-62]. There are over 35 nutrients in the Recommended Dietary Allowances, all with specific functions to maintain bodily activities. Many have intricate interrelationships with other nutrients during metabolism.

We were curious about the lack of nutritional intervention and asked "why"? Was it perhaps due to an antiquated belief promulgated in the last century that the fetus was the "perfect parasite" and its survival was based on its believed ability to usurp from maternal nutrient stores what it needed for sustenance? [119,120] Or was this omission simply due to inadequate nutrition education in medical schools? Adams et al. reported in a 2005 survey 51% of medical students described the emphasis in nutrition education as "inadequate". A recent survey conducted by ESPEN (originally the European Society of Parenteral and Enteral Nutrition, now known as the European Society of Clinical Nutrition and Metabolism) found similar assessments in many European universities [121-124]. Since little discussion was provided in most reports about nutrition screening or nutritional assessment, might this omission be because none of the current nutrition screening tools provides parameters to screen for malnutrition in obstetrical populations?

We reviewed the components of the various malnutrition screening and assessment tools mentioned earlier. The basic features to screen for malnutrition are weight loss and energy deficiency. Nutrition-related indicators were features of the MNA-SF, MST, MUST, Simple 2-Part, NST/BAPEN, NRS-2002 and SNAQ. Medical history which included weight changes, nutrition intake, GI symptoms, functional capacity, metabolic stress from disease was included in the SGA (subjective global assessment). Unintentional weight loss, decreased nutritional intake, functional capacity and chronic illness, acute illness or social behavioral/ environmental circumstances were included in the medical history component of AND/ASPEN. Unintentional weight loss (inclusive of decreased food intake, appetite loss, nutrient requirement/intake imbalances) were part of the ESPEN method, as well as reduced BMI <18.5, low fat free mass and unintended weight loss > 10% without a defined time or >5% over the last 3 months.

Some malnutrition screening tools include Inflammation as a component of malnutrition, however the best laboratory tests used to detect the presence of inflammation are considered investigational [17]. Various inflammation factors have been identified with HG, but no consensus has been reached to determine which to use in pregnancy and how they might be managed [125,126].

Nutrition modalities to address malnutrition in pregnancy have existed for years. Hew and Deitel first used total parenteral nutrition (TPN) in the US to attenuate the malnutrition of HG in 1980 [127]. Enteral nutrition feedings have successfully been implemented in HG [128-138]. Both nutrition modalities, enteral and parenteral, are commonly employed in NICUs to sustain prematurely born neonates as well as in medical and surgical units to feed those unable to take adequate oral nourishment.

Strengths

We believe our paper is the first to draw attention to a major omission in malnutrition screening and issues a clarion call for a multi-disciplinary conference to create criterion for gestational malnutrition because babies born to malnourished mothers begin their lives physically and cognitively compromised which adds to future health care costs, the frequent need for special education, lost productivity, and reduced quality of life. This paper may be the first to suggest deficiencies of major maternal electrolytes, coupled with severe weight loss and malnutrition may explain the high rate of pregnancy loss, which the timely provision of nutrition can mitigate.

Limitations

For our review, we only accessed one database (PubMed) which may not have captured all the current cases of the HG-WE

complex since 2019. We also searched PubMed for etiologies to explain the high rate of 50% IUFD rates which is associated with HG-WE but failed to locate any specific data. Potential etiologies include severe maternal starvation, chronic dehydration, various electrolyte deficiencies and thiamin depletion because of HG and/or a combination of several factors. Additional research is needed.

Conclusions

We coined this condition "gestational malnutrition" since it begins with pregnancy as do several other complications of pregnancy including "gestational diabetes", "gestational hypertension", "gestational thrombocytopenia", and "gestational hypothyroidism". It is hoped the "gestational" nomenclature will result in a rapid integration of malnutrition in pregnancy into the medical education of obstetricians, gynecologists, pediatricians, neonatalogists, midwives, as well as medical students who have aspirations in reproductive medicine.

To curtail inadequate nutrition during the most vulnerable period in the life cycle, malnutrition screening must be inclusive of pregnant women in clinics, emergency departments as well as inpatient arenas. We propose modifying the current AND/ASPEN criteria of weight loss and days of inadequate intake as amended to the AND/ASPEN documents in Table 7 and Table 8 (Table 7 and 8 here).

Pregnancy weight loss TO includes PRE-HYDRATION weight loss occurring during the gestation PLUS lack of expected weight gain per IOM.

The AND/ASPEN screening criteria for malnutrition, in collaboration with ESPEN and other dedicated nutrition support organizations, can become an effective vehicle for generating gestational malnutrition awareness. Inclusions are highlighted and bolded. First, the assessment of the ill gravida needs to contain baseline nutrient needs- energy and protein. Second, weight loss needs to be articulated in a two-step fashion: gross weight loss (taken before hydration therapy commences) and net weight loss, which add into the equation the expected IOM/NAS gain by gestational age and BMI, as per the examples provided in Table 2. Third, the screening documents need to include the word "pregnancy". Finally, RFS should be anticipated in situations where aggressive nutrition is applied in the setting of severe maternal weight loss with probable catastrophic consequences also to the fetus if it occurs.

As depicted in the fetal development graphic, Figure 2, embryonic development is progressive and is not reversible. Most vital organ systems begin forming in the first weeks of the first trimester. Correcting a nutrient deficit after the insult has occurred will not rectify the cerebral and/or anatomic injury.

Used with permission. OTIS. Adapted from Moore 1993 and the National Organization on Fetal Alcohol Syndrome (NOFAS.) [113].

Table 7: Modified AND/ASPEN Weight loss criteria for Malnutrition, including pregnancy.

Malnutrition criteria	Non-severe/moderate malnutrition	Severe malnutrition
	Weight loss	Weight loss
Acute illness/injury	1-2% in 1 week, **including pregnancy**.	>2% in 1 week, **including pregnancy.**
(Acute defined with no specific time)	5% in 1 month, **including pregnancy**.	>5% in 1 month, **including pregnancy.**
	7.5% in 3 months, **including pregnancy.**	**>**7.5% in 3 month, **including pregnancy.**
Chronic illness	5% in 1 month, **including pregnancy**.	>5% in 1 month, **including pregnancy.**
(Chronic defined as ≥ 3 months	7.5% in 3 months **< 7.5 months in 3 months if pregnant**.	>7.5% in 3 months. **< 7.5% in 3 months if pregnant.**
	10% in 6 months. <**10% in 6 months if pregnant.**	>10% in 6 months. **<10% in 6 months if pregnant.**
	20% in 1 year. **<20% in 1 year if pregnant.**	>20% in 1 year. **<20% in 1 year if pregnant.**
Social/environmental circumstances	5% in 1 month **including pregnancy**.	>5% in 1 month **including pregnancy.**
	7.5% in 3 months **including pregnancy.**	>7.5% in 3 months **including pregnancy.**
	10% in 6 months **including pregnancy.**	>10% in 6 months **including pregnancy**.
	20% in 1 year	>20% in 1 year

Table 8: Modified AND/ASPEN Energy Deficit Criteria for malnutrition, inclusive of pregnancy.

Malnutrition etiology	Non-severe/moderate malnutrition	Severe malnutrition
Acute illness/injury (acute defined with no specific time.)	< 75% of estimated energy requirements for > 7 days, including pregnancy. **Pregnancy requires scheduled re-assessment of malnutrition.**	≤ 50% of estimated energy requirements for > 7 days, including pregnancy. **Pregnancy requires scheduled re-assessment of malnutrition**.
Chronic illness (Chronic defined as illness ≥ 3 months.)	≤ 75% of estimated energy requirements for ≥ 1 month, **including pregnancy.**	≤ 75% of estimated energy requirements for ≥ 1 month, **including pregnancy.**
Social/environmental circumstances	< 75% of estimated energy requirements of > 3 months, **including pregnancy.**	≤ 50% of estimated energy requirements for ≥ 1 month, **including pregnancy.**

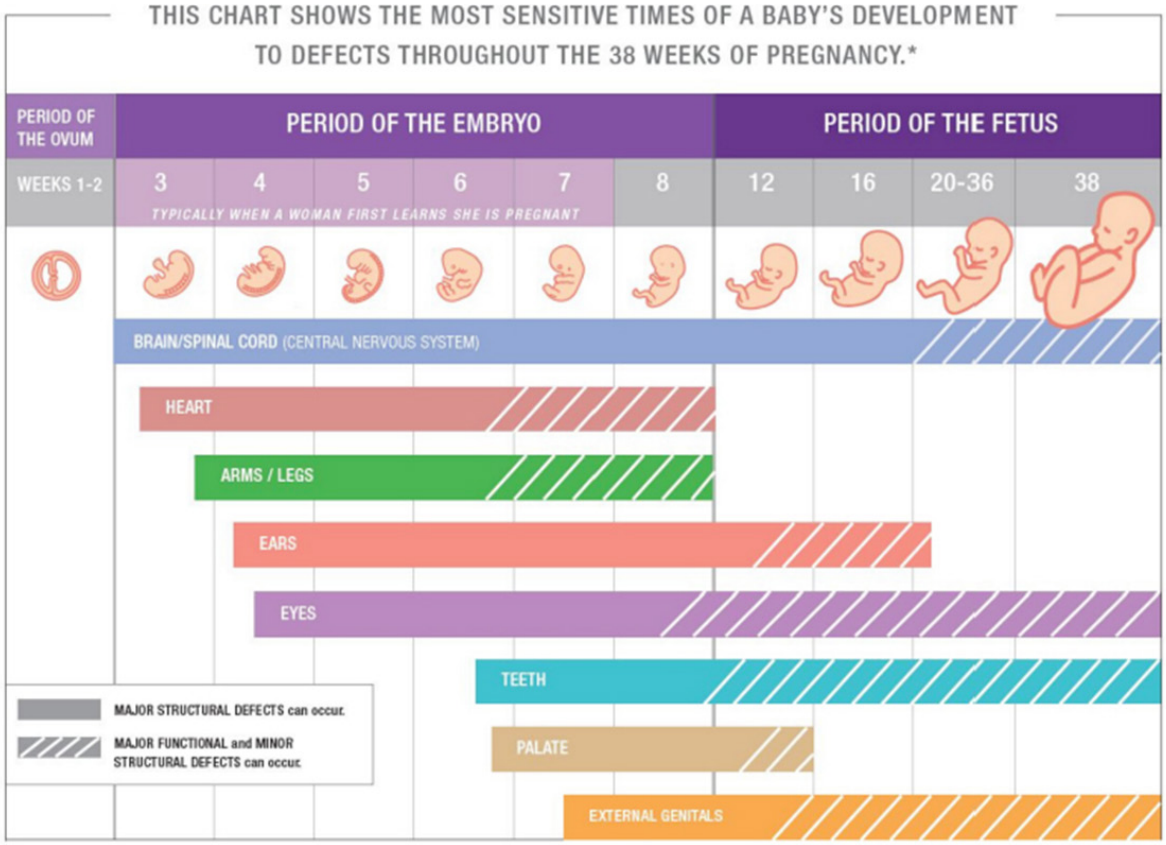

Figure 2: Fetal development from conception to term.

Malnutrition is known to be lethal. Meguid described an 18 year old gentleman who was admitted to a metropolitan tertiary teaching medical center with a fractured femur after a fall to the ground from a botched B&E—breaking and entering event [139]. The well-muscled gentleman weighed 150 pounds on admission, was treated for his injuries and bedded in a general medical ward. While his diet was described as non-restrictive, his oral intake was minimal and he received 3 liters/day of a dextrose solution, totaling 510 calories. The patient expired on HD 30 with the autopsy revealing a grossly emaciated body but a well healed femoral fracture. His weight loss was slightly over 20% of his admission weight in 1 month [139].

We have demonstrated malnutrition in pregnancy has consequences. We speculate this problem exists as there is no screening criteria to herald the nutritional deficits of the gestational dyad. Having no screening criteria provides no guidelines for remediation. Nutritional care is considered a basic human right—which includes the pregnant woman and her developing fetus [140]. The known published cases of HG-WE to date is 216 gravidas, which indicates at least 216 fetuses were additionally nutritionally deprived.

There is an urgent need to convene an international multidisciplinary committee to address this nutritional neglect. Until there are criteria to screen, classify and effectively treat gestational malnutrition, it will continue to be a skeleton in the closet.

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