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Long Term Consequences of Severe Hyperemesis Gravidarum Including Possible Intrauterine Fetal Demise

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Abstract

One in three cases of severe hyperemesis gravidarum (HG) results in early spontaneous abortion, however these losses remain inadequately investigated. Literature suggests pregnancies experiencing nausea and vomiting of pregnancy (NVP) experience fewer miscarriages. However, HG researchers document higher rates of preterm delivery and small for gestational age (SGA) neonates with increased morbidity. Women with severe hyperemesis are reassured of a successful outcome from results generated from NVP but question the biologic plausibility of fetal development in a severe catabolic state. Long term consequences of food blockades of WWII as well the 1959-1961 China famine document adult metabolic disease in offspring exposed to developmental malnourishment. The "fetus is a perfect parasite" myth is ill-founded as a malnourished mother simply cannot share absent substrate.

Key words: Gestational Malnutrition; Fetal Death; Starvation

Introduction

One in three cases of severe hyperemesis gravidarum (HG) results in early spontaneous abortion (SAB) or intra-uterine fetal demise (IUFD) however the etiologies of these losses remain inadequately explored. [1,2] This contrasts to late losses investigated for preventive aspects. [3] Literature suggests pregnancies with nausea and vomiting of pregnancy (NVP) have lower rates of miscarriage. [4] However, HG researchers report higher incidences of preterm delivery, small for gestation (SGA) neonates and increased neonatal and maternal postpartum morbidity. [5,6]

We believe the combination of severe maternal vitamin and mineral deficiencies, prolonged energy deficit and chronic dehydration contribute to some SAB or IUFD as illustrated in Figure 1. SAB is defined as a pregnancy loss before 12 6/7 weeks. [7] The terms SAB, miscarriage and early pregnancy loss are often used interchangeably. IUFD is the clinical term for stillbirth and describes the death of a fetus at or after the 20th week of gestation but IUFD is defined differently around the world, based on the gestational age and weight of the fetus. Twenty five to 60% of stillbirths are unexplained [8]. Forty percent of stillborn fetuses exhibit intra-uterine growth retardation (IUGR). [9]

The myth that the "fetus is a perfect parasite" is ill-founded. A malnourished mother/host cannot share nutrients and energy she does not possess. If fetal growth occurs in the setting of compromised nutrition, it may be at a reduced rate. [10] When protein is used for energy, there is a deficit of amino acids resulting in reduced cell formation in the embryo.

Growth failure in utero can be intrinsic or extrinsic. In intrinsic growth failure, placentas are of normal size implying that retardation of fetal growth was not caused by inadequate maternal-fetal transport but was the result of other factors, including chromosomal abnormalities, certain drugs that cross the placenta and maternal infections. [10] Extrinsic growth restriction manifests with smaller placentas with decreased capacity to supply adequate nutrition. Extrinsic growth retardation is either asymmetrical or symmetrical. Fetuses subjected poor transfer of nutrients and/or oxygen because of placental vascular insufficiency show asymmetrical growth with normal brain sizes and head circumferences. Liver size is reduced 50% with depleted glycogen stores causing extreme hypoglycemia at birth. [10] However, fetal hepatic glycogen stores are significantly different between asymmetric vs. symmetric growth failure. It has been observed that hepatic glycogen stores are reduced 100% in asymmetrical growth restriction in contrast to 20% reduction in symmetric growth failure. [11]

When nutrient restriction is imposed throughout most of gestation the pattern of growth retardation becomes more symmetrical. There is a decrease of 15-20% in cells affecting all organs including the brain with reduced head circumference. [11] Inadequate gestational nutrition impacts cognitive, skeletal and vital organ maturation, forming the foundation of Developmental Origins of Health and Disease (DOHaD). [12] Maternal protein-energy malnutrition reduces intakes of iron, zinc, iodine, folate and vitamin A. These nutrients are among the most critical for the developing brain and their absence results in substantial injury. [13]

The Recommended Dietary Allowances (RDAs) recommend increases in pregnancy, including caloric increase of approximately 18% (340 calories/day) in the second trimester and 23% (452 calories/day) in the third trimester as well as protein, omega 3 fatty acids, vitamins and minerals. There is no

recommendation for a hypo-caloric state in pregnancy, however it is well documented women with HG frequently fail to achieve nutritional adequacy. [6]

Compounding the nutrient detriment from HG is a substantial economic liability to health care. In 2012 US expenditures amounted to $ 1,778,473,782 with direct costs of $ 1,062,847,276 (60%) and indirect costs of $ 715,626,506, averaging of $ 1,827.00 per sick woman. [14].

Methods

We developed a hypothesis of key components of severe maternal nutrition deprivation leading to lethal fetal compromise. These inter-related components are depicted in (Figure 1). An exhaustive review of the medical literature provides credible evidence.

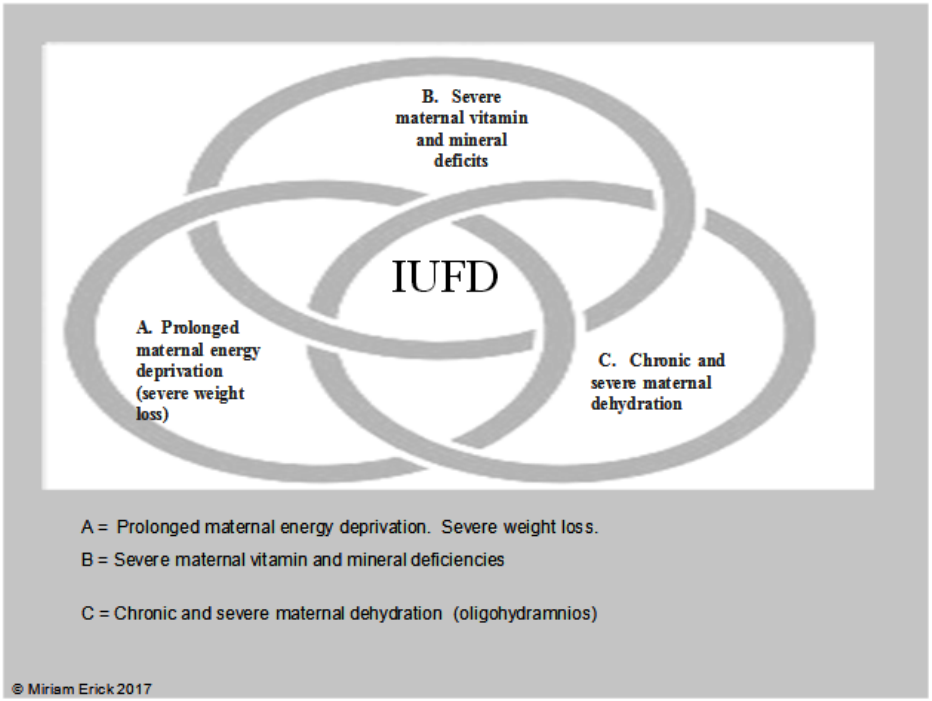

Figure 1: Potential maternal deficits contributing to some spontaneous abortions (SAB) and intrauterine fetal demises (IUFDs).

Discussion

A successful pregnancy requires a healthy woman, the absence of complications developing during gestation and adequate nutrition including energy, protein, vitamins, minerals, and fluid. Energy contributions are provided by the macronutrients carbohydrates, proteins, fats and alcohol, which is excluded due to teratogenesis. Vitamins and minerals, critical in growth and development, provide no energy value. Water, an essential nutrient, also provides no energy value, but is the largest single component of the body. [15].

In the adult, loss of 20% of total body water (TBW) results in death and a loss of 10% causes functional disorders. [15] A small percent of TBW (3%) is found in cerebral spinal, pleural, and pericardial fluids. Most of the water is distributed in two main components; intracellular water (ICW), which is contained within cells, makes up 2/3 of TBW. Extracellular water (ECW) is estimated to account for 1/3 of TBW or 20% of body weight. ECW is found in plasma, lymph, interstitial fluid, various secretions and in pregnancy, as amniotic fluid.

Inadequate maternal hydration decreases amniotic fluid volume and severe oligohydramnios contributes to fetal compromise. [16,17] The importance of adequate hydration is illustrated by a comparison: in moderate weather, adults can survive without water for only 10 days but can survive several weeks without food. [15]

Prolonged and Severe Maternal Energy Deprivation

Prolonged maternal energy deprivation results in weight loss. [5,6] In the absence of adequate maternal nourishment or increased nutrient losses, both occurring in hyperemesis gravidarum, a catabolic state emerges. Maternal muscle mass and adipose tissues are depleted. [18] Deficits of energy, vitamins and minerals exert developmental injuries on the growing embryo, with high rates of adult schizophrenia documented among offspring conceived during WW II food blockades as well as the Great China famine of 1959-62. [19,20]

In the setting of low glucose availability due to either starvation or insulin deficiencies in diabetic ketoacidosis (DKA),

there is a deficiency of pyruvate entering the citric acid cycle due to depletion of glycogen stores. Alternative energy is provided by the generation of acetyl Co A, from beta oxidation of fatty acids. When acetyl Co A production exceeds the capacity of the citric acid cycle, large amounts of beta hydroxybutyrate (BHB), acetoacetate and acetone, contributes to metabolic acidosis. In a healthy individual starvation of at least 14 days is required to reach maximum severity and pH falls < 7.3. Severe starvation produces ketones, resulting in an anion gap and metabolic acidosis. Severe metabolic acidosis with blood pH < 7.3 resulting in cerebral changes such as coma and confusion and increases the potential for cardiac irregularities and death. Limited data from postmortem biochemistry revealed extremely high levels of BHB in 5 adult subjects autopsied after death from starvation with levels ranging up to 8800 um/L, normal ranges being 1500-3500um/L. [21].

Acidemia in pregnancy with umbilical cord blood pH <7.0 or base deficit ≥12 mmol/L is associated with adverse fetal outcome, including death. Combined outcome of death or cerebral palsy was 3%, 10% and 40% at lowest pH of 6.9-6.99, 6.8-6.89 and <6.8, respectively, and 8%, 14% and 59% at a base deficit of 12-15.9, 16-19.9 and 20 mmol/L or more, respectively. [22]

Fetal metabolic demands accelerate biochemical change. Significantly higher levels of free fatty acids and BHB occur after 12 hours of fasting in pregnant women in the third trimester indicating "accelerated starvation". [23] Significant metabolic changes of a 41- year old woman, gravida 6 para 5, admitted to an intensive care unit (ICU) with 4 days of recurrent vomiting at 32 weeks of gestation are displayed in Table 1 [24]. Worsening Kussmaul's breathing, deep and labored respirations resulting in gasping, necessitated intubation and mechanical ventilation. Initially normal saline supplemented with thiamine and folic acid was provided with intravenous fluids but changed to 5% dextrose in lactated ringers to avoid hyperchloremic acidosis. Pregnancy continued successfully after this episode was resolved.

Table 1: Metabolic changes in a pregnant woman admitted to an intensive care unit (ICU)

Lab	Normal range	At admission	After 12 hours	After 24 hours	After 48 hours
pH	7.35-7.45	7.158	7.199	7.248	7.403
P CO_2	35-45 mm Hg	19.0	8.8	20.6	24.1
P O_2	80-100 mm Hg	24.9 (venous)	135	246	187
HCO_3^-	22-80 mEq/L	5	4	10	16
Anion gap	3-11 mmol/L	31	29	16	12
Lactate	0.5-1.0 mmol/L	1.4	1.0	1.0	1.0

Nutrition intervention can attenuate IUGR. Interventions involving a 33-week growth restricted fetus with oligohydramnios employed a daily therapy of amino acids at 5 ml/hr and 10% glucose solution, 25 ml/day, infused at 10% estimated feto-placental blood volume per day, improved growth in 5 weeks. The SGA female newborn born at 38 weeks gestation weighed 2130 g and measured 47 cm at delivery with Apgar's of 8 and 8 at one and five minutes. [9] The average 38-week neonate weighs 3083 grams and measures 49.8 cm. [25].

Severe calorie deficit results in critical lean body mass loss, including cardiac and respiratory muscles, contributing to death. Death occurred in a previously well-nourished adult male described as having "six-pack abs" on admission who suffered the metabolic trauma of a femur bone fracture after a weight loss of 20% during a hospitalization of 30 days and a prisoner succumbed after a 50-day hunger strike experiencing 26% weight loss with complications of Wernicke's Encephalopathy (WE). [26,27] A woman with pregravid BMI of 19, pregnant with IVF twins, died from respiratory failure after 14 weeks of hyperemesis, commencing at 6 weeks, experiencing a weight loss of 15% from her initial starting weight. An autopsy concluded a diagnosis of diffuse leukoencephalopathy. [28]

Severe maternal vitamin and minerals deficits

Vital organs, especially the brain, contain vitamins and minerals that are involved in metabolic functions. Nutrients from animal brain provides a comparative proxy for the adult brain as detailed in (Table 2). [5] Many neurotransmitters are generated from amino acid precursors including serotonin (5-hydroxy tryptamine), catecholamines, histamine, glycine and acetylcholine. [28]

The brain is an obligate glucose consumer with thiamine being a required co-factor in 3 enzymes involved in energy-metabolism via the pentose phosphate pathway. Thiamine deficiency results in a decrease in the levels of the putative neurotransmitters glutamate and aspartate, due to decreased entry of pyruvate into the tricarboxylic cycle. The effects of severe water-soluble vitamin deficiencies on the central nervous system are expressed by well-recognized alterations in behavior as pellagra related dementia due to niacin deficiency and WE related to thiamine deficiency. While thiamine deficiency is cited as the etiology of WE, other unmet nutrient requirements of the brain may co-contribute to WE as detailed in Table 2.

Table 2: Probable nutrients in the adult human brain* (proxied from nutrient data of beef brain)

Nutrient	Approximated amount* in 2.5-3-pound human brain
Water	70% weight of the adult brain
Cholesterol	27.9 grams
Energy-producing substrates	
Protein	155 grams
Fat (saturated)	41 grams
Fat (polyunsaturated)	32 grams
Fat (monounsaturated)	56 grams
Carbohydrates	Essentially none
Fat soluble vitamins	Provides no calories
Vitamin A	None identified
Vitamin D	Vitamin D receptors found
Vitamin E	32 mg
Vitamin K	None identified
Water soluble vitamins	Provides no calories
Thiamine (B1)	1.1 mg
Riboflavin (B2)	2.4 mg
Niacin (B3)	14 mg
Pyridoxine (B6)	3.4 mg
Folate (B9)	98 mcg
Cobalamin (B12)	120 mcg
Biotin	None identified
Ascorbic Acid (vitamin C)	14 mg
Pantothenic acid	15 mg
Choline	None identified
Minerals or electrolytes	Provides no calories
Calcium	126 mg
Copper	3.4 mg
Iodine	None identified
Iron	31 mg
Magnesium	210 mg
Phosphorus	4.9 grams
Potassium	3.4 grams
Sodium	1.7 grams
Selenium	None identified
Zinc	17 mg

Beef brain nutrient content. USDA National Database for Standard Reference Release 27. (5)

Thiamine deficiency is causative in the development of WE, a potentially lethal condition affecting neurological, cardiac and muscle function in affected individuals. Maternal Wernicke's confers a high rate of fetal loss. The fetal mortality was found to be 33.3% among 49 cases of women suffering severe both HG and WE. [2] Weight loss averaged 11.77 kg with an illness of 7.7 +/- 2.8 weeks. IUFD following WE suggests thiamine depletion likely impacted the fetus. [29] The half-life of thiamin is 9-18 days and deficiency can occur within 14-20 days in the setting of inadequate intake. [30]

Inadequate nutrients contribute to skeletal muscle compromise. Combined nutrient deficiencies of selenium (Se) and vitamin C accelerated injuries in doubly deficient guinea pigs. [31] Four groups of weaned male guineas pigs were studied

for 3 weeks: controls, vitamin C deficient, Se deficient and both vitamin C and Se deficient. Deficiencies were confirmed by determinations of glutathione peroxidase activity and vitamin C concentrations in liver and skeletal muscles. The combined Se and vitamin C deficiencies resulted in more severe skeletal muscle cell injury than that caused by selenium deficiency alone [32].

Vitamin K deficiency has been reported in HG, resulting in fetal subdural hematoma (SDH) (and chondrodysplasia punctata. [33,34] Vitamin K has dual roles: coagulation and bone metabolism and both injuries have been observed in the fetus. Multiple reports of maternal vitamin K deficiency with subsequent adverse consequences exist.

Inadequate energy intake co-exists with vitamin, mineral and electrolyte deficiencies. Brain tissue is highly dependent upon an adequate supply of nutrients, especially phosphate, thiamine and glucose. The adult brain comprises 3% of body weight however requires 28% of daily energy. Estimates are that greater than 50% of the fetal energy expenditures is consumed by the developing brain. [13]

Phosphorus is required by all major vital organs including brain, heart, kidneys, lung and liver for energy metabolism as it is a key component of adenosine tri-phosphate (ATP) and critically involved in nucleic acid functioning and enzyme activity. [34] When aggressive nutrition is administered to a malnourished person without adequate repletion of electrolytes, serum electrolytes plummet as cells update nutrients. New tissue requires increased glucose, potassium, phosphorus, magnesium and other nutrients for growth. Low levels of electrolytes result in "Re-feeding syndrome", manifesting with lethargy, confusion, and weakness. If not corrected, cardiac irregularities, respiratory failure and death result. [35]

Low electrolytes can induce cardiac abnormalities especially prolonged QT intervals. ECG changes were reported in a 24-week pregnant woman with hypophosphatemia of 0.76 mmol/L and hypokalemia of 3.0 mmol/L after standard repletion, indicating a severe pretreatment nadir. The ECG reflected a prolonged QTc of 510 ms, (normal QTc is < 460 ms), indicating high risk for Torsade de pointes. Torsade can revert spontaneously to sinus rhythm or escalate to ventricular fibrillation with increased risk for cardiac arrest.[36] Hypokalemia in the mother increases the likelihood of cardiac irregularities in the fetus.

Fetal bradycardia (< 120 beats per minute) was documented in a pregnant woman with thiazide-induced hypokalemia at 38 weeks gestation. [37] An external fetal monitoring indicated fetal distress with fetal heart rate (FHR) between 65-70 bpm with a low maternal potassium of 3.3 mg/dL. (normal 3.5-5.0 mg/dL). After repletion, repeat potassium improved to 4.2 mg/dL, and FHR was confirmed at 130 bpm, suggesting maternal potassium depletion altered FHR.

Vitamin D deficiency has been associated with adult cardiac disease including dilated cardiomyopathy and documented in infants with complications of cardiomyopathy, myelofibrosis and hypocalcemic convulsions who have been breast-fed by vitamin D deficient mothers . [38-40].

Chronic and severe maternal fluid deficit/ dehydration

Maternal dehydration decreases amniotic fluid volume (AFV). [41] Six pregnant ewes water deprived for 54 hours demonstrated increased maternal plasma osmolality from 306.5 +/- 0.9 to 315.6 +/- 1.9 mOsm/kg and increased fetal plasma osmolality from 300 +/- 0.9 to 312.7 +/- mOsm/kg. AFV was reduced by 35%, from 871 +/- 106 to 520 +/- 107 ml. [17] Increased plasma osmolality may have contributed to extensive ventricular thrombus which was found in a dehydrated infant. [42]

Oligohydramnios, defined as AFV less than expected for gestational age, results in fetal deformations due to constricted uterine space, umbilical cord compression and death. [43] Amniotic fluid is critical for optimal fetal lung development, serves as a protective cushion against outside trauma and allows fetal movement within the uterine space. 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. [44]Cord compression decreases oxygen, energy and various nutrients to support growth and development of major organs, including brain, heart, lung, kidney and liver. [16,45-47]

Conclusion

Our hypothesis suggests fetal loss likely implicates severe deficits in three maternal compartments: energy, vitamins and minerals, and hydration as documented in Table 3. Each of these deficits can result in IUGR. IUGR has been found in 40% of stillborn fetuses. [9] The developing fetus is without nutritional reserve. What degree of maternal nutrition compromise leads to IUFD is unknown. Research demonstrates deficiencies during the fetal period have long-term consequences for neonate and future generations. The economic costs of developmental compromise due to gestational malnutrition is yet to be determined but likely increases financial burden of health care. In the meantime, supplying adequate nourishment for the mother simultaneously optimizes fetal well-being, endorsing the concept that "an ounce of prevention is worth a pound of cure".

LONG TERM CONSEQUENCES OF SEVERE HYPEREMESIS GRAVIDARUM (HG) INCLUDING POSSIBLE INTRAUTERINE FETAL DEMISE (IUFD): a plausible explanation.

Table 3: Potential maternal nutrient deficiencies involved in fetal loss
Maternal Energy Deprivation
↓ DHA → hypomyelination in the fetal brain → ↓ visual acuity and attention. (13)
↓ protein→ ↓ amino acids → ↓ fetal muscle development, including heart , respiratory and major organ function ↓ protein → ↓ amino acids → ↓ fetal neurotransmitters (29) (52)
↓ energy → maternal death due to loss of critical lean body mass (26) (27) (28)
↓ carbohydrates → poor maternal cognition (2) (53)
↓ energy → ketone development → acidemia →↓ IQ in offspring (22)
↓ energy → IUGR and/or SGA → ↑ neonatal morbidity (54)
Maternal Vitamin and Mineral Deprivation
↓ vitamin A → ↓ fetal retinal, renal and pulmonary development, growth (55) (56) (57)
↓ vitamin D → ↓ fetal skeletal metabolism, lung function (51)
↓ vitamin K → ↓ fetal skeletal maturation, ↓ coagulation -→ fetal subdural hematoma (SDH), intraventricular hemorrhage (IVH) (33) (34)
↓ phosphorus, potassium, magnesium → ↓ maternal cardiac and respiratory muscle contractility, death (35)
↓ thiamine →↑ maternal Wernicke's encephalopathy →↑ maternal death (2)
↓ vitamin B 12 → ↑ neurological failure in fetus, failure to thrive in neonate (52)
↓ vitamin D → ↓ thymus development, dilated cardiomyopathy (41) (58)
↓ iron → ↓fetal oxygen-carrying capacity and ↓ myelination (59) (60)
↓ vitamin C → ↓ fetal collagen development, compromised vascular integrity, (61) (62)
↓ vitamin C → ↓ placenta growth (63)
↓ choline → ↓ acetylcholine, an important neurotransmitter (29)
↓ phosphorus → ↓ maternal/ fetal brain ATP (36) (62)
Maternal Dehydration (resulting in oligohydramnios)
↑ dehydration →↑ amniotic fluid osmolality (42) increased possibility of fetal venous thrombosis (43)
↓ amniotic fluid volume → ↓ fetal movement via ↑ constriction (16)
↓ amniotic fluid→ ↑ umbilical cord compression (47)
↑ umbilical cord compression → ↓ fetal O_2 delivery → ↑ acidemia (16) (47) (48) (64) (65) (66)
↓ maternal blood volume → ↓ fetal nutrient delivery (45)
↓ amniotic fluid volume → ↓ fetal lung development (46)
↓ brain angiotension system contributing to dipsogenic changes (67)

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