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Complications of Hyperemesis Gravidarum; A Disease of Both Mother and Fetus, Review Article

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Abstract

Hyperemesis Gravidarum (HG) is the most severe form of nausea and vomiting during pregnancy and is characterized by severe intractable nausea and vomiting that lead to many maternal and fetal consequences. HG is mainly diagnosed clinically; most of the physicians diagnose it by its typical clinical picture and exclusion of other causes of nausea and vomiting in the pregnant woman. Nausea and vomiting are a disease of high prevalence among pregnant women and it is a common experience affecting 50-90% of all women. It is the most common indication for hospitalization during the first half of pregnancy. HG occurs in only about 0.5-2% of cases but actually, when it occurs it may be associated with morbidity of both mother and fetus. Adequate replacement therapy and weight gain may prevent most of the maternal and fetal consequences. Pregnant women with HG may suffer marked psychosocial burden. Moreover, the condition may be complicated by electrolyte imbalances, nutritional deficiencies, and Wernicke's encephalopathy. Other complications include thrombosis, esophageal trauma, cerebral vascular spasm, others are related to TPN and central venous lines. Besides, recurrence of HG in subsequent pregnancies may occur.

Offspring of pregnant women with HG may suffer long-term conditions which include high serum cortisol, decreasing insulin sensitivity, high risk of mood and psychiatric problems. Studies showed no significant increase in the incidence of congenital anomalies among these neonates versus the control group. Regarding cancer, the large Scandinavian study found no association between HG and incidence of 12 types of childhood malignancies, only increased the incidence of lymphoma and testicular tumor was found which need further studies to confirm this causal relation. Besides, higher incidence of preterm labor, placental abruption, preeclampsia and small for gestational age were found in these patients. Further studies are needed to determine long-term maternal complications and to study long-term effect of HG on the mental and physiological status of offspring of HG mothers during adulthood.

Keywords: Hyperemesis gravidarum; Complications; Maternal; Fetal

Abbreviations:

HG: Hyperemesis Gravidarum; RCOG: Royal College of Obstetricians and Gynecologists

Introduction

Hyperemesis Gravidarum (HG) is the most severe form of nausea and vomiting during pregnancy that leads to many maternal and fetal consequence [1] that may include dehydration, electrolyte, and metabolic disturbances and nutritional deficiency, that may require hospitalization [2,3]. HG is mainly diagnosed clinically, most physicians diagnose it by its typical clinical picture and exclusion of other causes of nausea and vomiting in the pregnant woman [2]. The onset of vomiting typically starts between 6 and 8 weeks gestation and peaks by 12 weeks [4]. Nausea and vomiting is a disease of high prevalence among pregnant women. Also, it is a common experience affecting 50% to 90% of all women [5]. It is the most common indication for hospitalization during the first half of pregnancy but incidence of HG varies from 0.5% to 2% [3] nausea and vomiting are usually limited to the first trimester but 20% of women continue throughout pregnancy [6] There are many complications of HG that may affect both maternal health status. Moreover, many studies point to certain effects of HG on the fetus in utero. Further studies are needed to determine long-term maternal complications [6] and to study the long-term effect of HG on the mental and physiological status of offspring of HG mothers during adulthood [7].

Maternal Complications

Psychological impacts

Studies have shown that the psychological and social effects of hyperemesis may be underestimated [8]. Pregnant women with HG, particularly severe HG, are at potential risk of cognitive, behavioral dysfunction and emotional stress in

pregnancy [9]. The causal relationship between HG and this psychological stress has yet to be explored. In an observational study, 50.5% of pregnant women with HG were found to have potential psychiatric troubles. The severity of vomiting is correlated with social dysfunction, anxiety, sleep disorders and severe depression [3]. Patients with HG were more likely to report that their health care providers did not realize how their illness was severe. Many patients with hyperemesis reported fear of subsequent pregnancy due to their experience with this condition [8]. That is why health providers play a critical role in counseling pregnant with HG and help them to accept pregnancy and the disease [5]. The patient should be informed that with adequate replacement therapy and adequate weight gain, all fetal and maternal consequences are preventable [10]. In fact, failure of providing support and empathy to those patient contributes to their decision of termination of a planned pregnancy [11].

Nutritional deficiency

In women with HG, The mean intake of most nutrients in diet falls below 50% of the recommended dietary intake. More than 60% of patients with HG have relative insufficiency of thiamine, riboflavin, pyridoxine, retinoic acid, and retinol-binding protein. Therefore, the hyper-emetic pregnant patient is at nutritional potential risk, and early initiation of corrective supplementary and therapeutic treatment is recommended in order to avoid serious and potentially irreversible damage [3].

Clinically significant deficiencies of the fat-soluble vitamins, especially vitamin K, have been reported, this has been linked to adverse effects such as neonatal hemorrhage. Many cases reported the development of coagulopathy from vitamin K deficiency that contributed to intraperitoneal hemorrhage intraoperatively in those women with large myoma and small bowel obstruction that had been diagnosed with hyperemesis and underwent operation during pregnancy. This coagulopathy might cause increased blood loss during procedures and surgeries required during pregnancy [8]. Also, deficiencies of vitamin B6 and B12 have been reported and lead to anemia and neurological problems [12]. Folic acid replacement should be administered until symptoms are improved in order to prevent the incidence of neural tube defects in the fetus and more doses are required for high-risk patients [2,13].

Wernicke encephalopathy

Wernicke's encephalopathy is a rare condition but it is well recognized and distressing complication of severe HG resulted from thiamine deficiency [2]. It can be precipitated by carbohydrate-rich food but it commonly occurs in cases of thiamine deficiency who received glucose infusions without thiamine replacement which deteriorates the suboptimal biochemical status of thiamine [14]. The two of three maternal deaths that were attributed to hyperemesis reported in the Confidential Enquiries into Maternal Deaths in the United Kingdom 1991-1993 were due to Wernicke's encephalopathy [15]. A recent review of Wernicke's encephalopathy resulting from hyperemesis suggested that it normally manifests after

approximately 7 weeks of vomiting and feeding difficulties at around 14 weeks of gestation [16].

Diagnosis of Wernicke's encephalopathy is mainly a clinical diagnosis. Although the classic triad of this condition (confusion, ocular abnormalities, and ataxia) occurs in only 46.9% of the patients, the majority of patients manifested only by one of these symptoms. Thus, there should be a low threshold of suspicion of Wernicke's encephalopathy in the pregnant patient with a history of hyperemesis and any neurological symptoms or behavioral changes should be managed seriously [17]. Moreover, the overall pregnancy loss rate (both spontaneous and planned termination) attributable to Wernicke's encephalopathy was 47.9% [3]. Common laboratory findings include raised liver enzymes and low RBC transketolase which is a thiamine-dependent enzyme [18]. MRI is the gold standard investigation and typically demonstrates symmetrical lesions around the aqueduct and fourth ventricle affecting mammillary bodies [19]. In the series reported by Chiossi, et al., complete resolution of Wernicke's encephalopathy occurred in only 14 of 49 patients as symptoms' resolution may require months and permanent disabilities were common [4,7,11,12].

In many case reports, patients who received TPN without thiamine in the mixture are complicated with iatrogenic Wernicke encephalopathy so it is important for health care providers to ensure adequate thiamine replacement [8]. Currently, RCOG recommends using Ringer's and Lactate infusions more than glucose infusion [20-22].

Electrolyte imbalance and metabolic disturbances

Hyponatremia (plasma sodium levels <120 mmol/L) has occurred as a complication of HG. Clinical features of mild hyponatremia are nonspecific and may include anorexia, headache, nausea, vomiting, and lethargy. This presentation may be difficult to be distinguished from symptoms of HG itself. More pronounced hyponatremia may result in personality changes, muscle cramps, and weakness, confusion, ataxia, drowsiness, diminished reflexes, and seizures. Rapid correction of hyponatremia is a very dangerous procedure. There is a relationship between rapid correction of plasma sodium and osmotic demyelination syndrome (central pontine myelinolysis) which is characterized by the loss of myelin in the pontine neurons and in other sites such as internal capsule, basal nuclei, cerebellum, and cerebrum. The classical symptoms of myelinolysis are spastic quadriparesis and pseudobulbar symptoms which indicate damage to pyramidal and corticobulbar tracts. Serious symptomatic hyponatremia is a medical emergency and needs to be managed appropriately by skilled personnel because the treatment may be potentially as dangerous as the condition itself [2,3].

Serum electrolyte imbalances of patients with hyperemesis may result in severe hypokalemia. Potassium abnormalities have been reported to increase the mortality in pregnant women with hyperemesis. Besides, severe hypokalemia may cause rhabdomyolysis in the setting of HG [8]. Potassium replacement should be done slowly and under monitoring in order to avoid cardiac arrest in diastole [23].

Other complications

Thrombosis: The coincidence of pregnancy, dehydration [2] and associated immobility in a woman with hyperemesis increase the risk of venous thromboembolic disease [3].

Esophageal injuries: Severe retching associated with attacks of vomiting in hyperemesis patients may cause esophageal trauma and Mallory-Weiss tears [2,3]. Retinal detachment, esophageal rupture, pneumo-mediastinum, and splenic avulsion have been reported as well [2]. While some patients with this complication may be managed conservatively, others may require surgical treatment. This complication may be considered in patients whose physical examination show subcutaneous emphysema at neck; also this sign may be seen in MRI neck and chest X rays [8].

Complications of TPN: Patients with HG who are unable to keep oral intake sometimes require TPN. Patients who require TPN for nutritional support are likely to require central line placement [24]. Central line catheters have been associated with complications such as infections, thrombosis, hematomas, pneumothorax and cardiac arrhythmias [8].

Vasospasm of cerebral arteries: Two pregnant women with severe HG refractory to intravenous fluid therapy and multivitamins replacement were reported to have vasospasm of the middle cerebral arteries by MRI. In both patients, vasospasm decreased after improvement of the hyper-emetic status. The authors concluded that an increased sympathetic nervous system activity with HG may contribute to the vasospasm [25].

Risk of recurrence: It is found by many studies that potential risk of recurrence of HG in subsequent pregnancy is higher in women with positive history of HG than in women without past medical history of HG, it is also found that women may choose to avoid subsequent pregnancies in order to avoid psychosocial impact of HG [26]. So a pre-conceptional counseling should be done in subsequent pregnancies [27]. Women with a past medical history of HG and their health care providers should discuss a management plan as a part of pre-conceptional treatment. Moreover, health care providers should plan a more frequent prenatal visit after diagnosis of pregnancy in order to facilitate more rapid diagnosis and prompt management. In addition, providers should identify individuals who have suffered from HG who may be afraid to get pregnant again for effective counseling pre-conceptionally [26].

For women without a history of hyperemesis in the first pregnancy, the risk in subsequent pregnancy increased with the prolonged interval between the two pregnancies. For women with a history of hyperemesis in the first pregnancy, no effect of the duration between the pregnancies was observed [27]. Similar relations have been observed in a previous study of recurrence of preeclampsia [28].

Fetal Complications

HG is a disease of pregnancy that needs more studies regarding not only short-term maternal physical and mental health problems, but also potential complications to the exposed fetus, especially if the fetus is exposed to this condition

early [29]. These fetal complications occur more frequently in pregnant women with HG who do not gain adequate weight of at least 7 kg as these complications are mainly related to lack of weight gain [30] rather than the disease itself [31]. HG has been also associated with smaller head circumferences in offspring, associations between smaller head circumference at birth and lower cognitive ability needs further studies [32]. Women with severe HG had a higher rate of spontaneous preterm birth compared to women without HG [3,22]. It has been also associated with low 5 minutes Apgar score in neonates [31]. Regarding congenital anomalies, data showed no significant increase in the incidence of congenital anomalies among neonates of HG mothers versus control groups [7].

Behavioral and psychic problems

A significant data supports an increase in the incidence of neurodevelopmental and behavioral diseases in children exposed to HG during pregnancy which indicates that HG may be associated with lifelong problems on the exposed fetus. The cause of this association needs to be well studied. It may be due to the patient's anxiety, disturbed hormonal levels during embryogenesis and/or abnormal maternal neonatal bonding post-natally or inadequate nutrition and vitamins deficiencies [29]. Millstones at the age of 1 year were not affected by HG [30]. But there is a higher risk of depression, bipolar disorder, and anxiety disorders during adulthood which is attributed to the HG itself, rather than to any other confounding factors linked to HG [33].

Insulin sensitivity

In addition to that, an increasing evidence supports long-term adverse outcomes associated with HG exposure may include a higher baseline of serum cortisol, a decrease of insulin sensitivity [29] a study of prepubertal children of mothers who experienced HG show higher serum cortisol and more reduction in insulin sensitivity than the control group [7]. But there are no studies investigate the further association with diabetes, coronary heart disease and stroke [34]. We are in need of these studies in the future to outline the consequences of this observation on offspring during adulthood.

Risk of malignancy

A large case-control study is performed in Denmark, Norway, and Sweden regarding risk of malignancy between offspring of hyper-emetic mothers versus well-matched control, this study found no significant increase of incidence of twelve childhood malignancies, there was only increase in incidence of lymphoma which was attributed to chance and author recommend more studies to confirm this association [35]. Two studies showed a higher incidence of testicular malignancy [36,37]. The association of HG and testicular malignancy of offspring is suggested to be due to hormonal disturbances which include higher levels of hCG and estradiol and both are associated with undescended testes, therefore this fact may contribute to a higher incidence of testicular malignancy among offspring [30].

Abnormal placentation

Pre-eclampsia, placental separation and small for gestational age are diseases of abnormal placentation. A large study in Sweden reported an association between HG and placental dysfunctional diseases which include the risk of preterm preeclampsia, abruptio placentae and small for gestational age. These diseases were mainly related to cases with HG hospitalized during the second trimester [38].

Summary

HG is a severe form of vomiting in pregnancy [3] which occur in only about 0.5 to 2% of cases [39] but actually when it occurs, it may be associated with morbidity of both mother and fetus. Adequate replacement therapy and weight gain may prevent most of the maternal and fetal consequences [40]. Pregnant women with HG may suffer marked psychosocial burden [3]. Moreover, the condition may be complicated by electrolyte imbalances [2], nutritional deficiencies [12] and Wernicke's encephalopathy [16]. Other complications include thrombosis [2], esophageal trauma [8], cerebral vascular spasm [25], others are related to TPN and central venous lines [24]. Besides, recurrence of HG in subsequent pregnancies may occur [26].

Offspring of pregnant women with HG may suffer long-term conditions which include high serum cortisol, decreasing insulin sensitivity [29], high risk of mood and psychiatric problems [29]. Studies showed no significant increase in the incidence of congenital anomalies among these neonates versus control group [7]. Regarding cancer, the large Scandinavian study found no association between HG and incidence of 12 types of childhood malignancies [37], only increased the incidence of lymphoma [37] and testicular tumor [30] were found which need further studies to confirm this causal relation. Moreover, higher incidence of preterm labor, placental abruption, preeclampsia and small for gestational age were found in these patients [38].

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