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HYPEREMESIS GRAVIDUM

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Abstracts

DEFINITION AND CLINICAL CHARACTERISTICS OF HYPEREMESIS

Defines hyperemesis gravidarum as persistent and excessive vomiting starting before the end of the 22nd week of gestation, and further subdivides the condition into mild and severe

. It is typically characterized by severe nausea and vomiting that causes dehydration and imbalances of fluid and electrolyte, disturbs nutritional intake and metabolism, causes physical and psychological debilitation, and often necessitates hospital care . The onset of vomiting usually occurs within the first 12 weeks of pregnancy. The Fairweather criteria define hyperemesis gravidarum as vomiting more than three times a day, weight loss, ketonaemia, electrolyte imbalance and volume depletion, with typical onset at 4–8 weeks of pregnancy and continuing

through to weeks 14–16 of pregnancy.3 However, it is not uncommon for hyperemesis to continue into the late second and third trimesters. The International Statistical Classification of Disease and Related Health Problems

EPIDEMIOLOGY

Patients with hyperemesis are more likely to be younger, non-smokers, and nonCaucasian. Hyperemesis patients are also more likely to have a multiple gestation and are more likely to have caesarean delivery.2 Other risk factors for hyperemesis include a previous history of hyperemesis, current and previous molar pregnancy, pre-existing diabetes, depression or psychiatric illness, hyperthyroid disorder, peptic ulceration or other gastrointestinal disorders, and asthma.6 The risk of admission for hyperemesis has been found to be 29 times higher if the previous pregnancy also featured an antenatal admission for hyperemesis.6 Several studies have found that smoking is associated with a reduction in the risk of hyperemesis.2,6,7 Maternal smoking before pregnancy is a significant protective factor against nausea and vomiting, even after consideration of maternal age and parity. If nausea and vomiting in pregnancy is an expression of a well-functioning placenta, the negative association with smoking may reflect the negative effect of maternal smoking on early placenta development.7 Vitamin supplementation during early pregnancy, but not before, also seems to protect against nausea and vomiting in pregnancy. The relation between the two is unknown.

AETIOLOGY OF HYPEREMESIS

The pathophysiology of nausea and vomiting in pregnancy has not yet been clearly elucidated. Hyperemesis involves a complex interaction of biological, psychological, and sociocultural factors. Various putative mechanisms have been proposed. Human chorionic gonadotropin In a review of 15 published prospective studies (1990–2004) investigating the relationship between human chorionic gonadotropin (hCG), 11 reported that there was significantly higher levels of serum hCG in hyperemesis patients than in controls.12 It is postulated that hCG causes hyperemesis via a stimulating effect on the secretory processes in the upper

gastrointestinal tract. Alternatively, hCG is structurally similar to thyroid-stimulating hormone (TSH) and possibly causes hyperemesis by stimulation of the TSH receptor (see below).13,14 Oestrogens Lagiou et al15 prospectively evaluated the role of oestradiol (E2), oestriol (E3), progesterone and prolactin in 262 pregnant women. They found that maternal serum prolactin levels are significantly inversely related to vomiting and/or nausea. They also reported a positive association between nausea and vomiting and maternal serum E2 levels. Nausea and vomiting are recognized side-effects of oestrogen-containing contraceptive preparations, providing further support for a link between oestrogen and hyperemesis in pregnancy. It has been proposed that elevated maternal serum levels of steroid hormones cause a decrease in intestinal motility and gastric emptying. This in turn alters gastrointestinal pH and encourages the development of subclinical Helicobacter pylori infection, which could be related to gastrointestinal symptoms.

Thyroid hormone

In early pregnancy, physiological stimulation of the thyroid gland occasionally leads to gestational transient thyrotoxicosis (GTT). GTT has been observed in up to two-thirds of women suffering from hyperemesis.17 Eleven of 15 prospective studies comparing thyroxine (T4) levels of hyperemesis patients with those of asymptomatic controls showed significantly higher T4 levels in the hyperemesis group. Moreover, nine of 13 prospective studies investigating TSH levels reported significantly higher TSH levels in the hyperemesis group.12 The production of thyroid-binding globulin increases under oestrogenic influence, and T4 metabolism is slowed. The transient decrease in free T4 level and higher renal iodine clearance causes stimulation of the thyroid to compensate for a relative iodine deficiency. Furthermore, hCG shares a common a-subunit with TSH, and the structural similarity can cause excessive stimulation of the thyroid gland.

Helicobacter pylori infection

Eleven prospective case–control studies have reported a significant increase in H. pylori infection in hyperemesis patients.12 One study using histological examination of mucosal biopsy, considered to be the gold standard diagnostic tool for testing H. pylori infection, reported that 95% of all hyperemesis patients tested positive for H. pylori compared with 50% in the control group. They also found significantly higher H. pylori densities in the gastric antrum and corpus in hyperemesis patients.

Psychosocial factors

In the past, severe vomiting during pregnancy was often perceived as an expression of maternal resentment towards her unwanted pregnancy. Various psychological stresses have been linked with hyperemesis, including emotional immaturity, strong motherdependence, and anxiety and tension related to the pregnancy. More recent investigators argue that the psychological symptoms are a result of stress arising from the physical burden of hyperemesis rather than a cause.

DIAGNOSIS AND INVESTIGATION OF HYPEREMESIS

Diagnosis &Investigations

may reveal hyponatraemia, hypokalaemia, low serum urea, raised haematocrit, metabolic hypochloraemic alkalosis, ketonuria, and increased specific gravity of the urine.20 A mild elevation of serum liver transaminase occurs in almost 50% of patients with hyperemesis, and it is thought to be associated with a temporary 758 S. K. Ismail and L. Kenny impairment of mitochondrial fatty acid oxidation.21 Transient hyperthyroidism (illustrated by elevated free thyroxine or suppressed TSH) occurs in approximately in two-thirds of women with hyperemesis.17 It is self-limiting, and thyroid function normalizes at 15–19 weeks of gestation.17,22 Patients are usually clinically euthyroid, and antithyroid treatment is inappropriate. In the rare event that clinical features of hyperthyroidism are demonstrated, thyroid antibodies should be assessed. Hyperemesis is associated with an increased placental load and is therefore more common in multiple and molar pregnancies. Ultrasound assessment of the pregnancy is a mandatory investigation.

COMPLICATIONS OF HYPEREMESIS

Malnutrition and vitamin deficiencies

The mean dietary intake of most nutrients falls below 50% of the recommended dietary allowances in women with nausea and vomiting in pregnancy.23 Cyanocobalamin Presentation: First onset of vomiting within 12 weeks gestation Prolonged nausea and vomiting Fluid and/or food intolerability Clinical dehydration Objective weight loss Ketonuria Previous history of Investigation: Urea and electrolytes Liver function test Urinalysis/mid stream urine Admission Day care Management and resolution of symptoms Additional investigation Full blood count Calcium Blood glucose Thvroid function test Inpatient Presentation: First onset of vomiting after first trimester History of other medical condition Consider other differential diagnosis Recurrence of symptoms Diagnosis . The diagnosis of hyperemesis. Hyperemesis gravidarum 759 (vitamin B12) and pyridoxine (vitamin B6) deficiencies may lead to anaemia and peripheral neuropathy. More than 60% of patients with hyperemesis gravidarum have suboptimal biochemical status of thiamine, riboflavin, vitamin B6, vitamin A, and retinol-binding protein. The hyperemetic pregnant patient is at nutritional risk, and prompt initiation of corrective therapy is recommended before serious and potentially irreversible damage occurs.

Wernicke's encephalopathy

Wernicke's encephalopathy is a rare but recognized and distressing complication of severe hyperemesis gravidarum caused by thiamine deficiency, and can be precipitated by carbohydrate-rich food and dextrose infusions. The two of three maternal deaths associated with hyperemesis reported in the Confidential Enquiries into Maternal Deaths in the United Kingdom 1991–1993 were due to Wernicke's encephalopathy. A recent review of Wernicke's encephalopathy resulting from hyperemesis suggests that it normally manifests after approximately 7 weeks of vomiting and feeding difficulties at around 14 weeks of gestation.24 The classic triad presentation of Wernicke's encephalopathy (confusion, ocular abnormalities, and ataxia) manifested in only 46.9% of the patients; the majority of patients exhibited only one of these symptoms. Thus, there should be a low threshold for suspecting Wernicke's encephalopathy in the pregnant patient with a history of hyperemesis and any neurological symptoms. In this series the overall pregnancy loss rate (both spontaneous fetal loss and planned abortion) attributable to

Wernicke's encephalopathy was 47.9%. The diagnosis of Wernicke's encephalopathy is clinical. Common findings include abnormal liver function and low red-cell transketolase (a thiamine-dependent enzyme). Magnetic resonance imaging is the gold standard investigation and typically demonstrates symmetrical lesions around the aqueduct and fourth ventricle. In the series reported by Chiossi et al24 complete remission of Wernicke's encephalopathy occurred in only 14 of 49 cases. Symptom resolution required months and permanent impairments were common. This emphasizes the importance of thiamine supplementation in the treatment of women with prolonged vomiting in pregnancy.

Depressive illness and psychological problems

Nausea and vomiting in early pregnancy are associated with psychiatric morbidity. The causal relationship between the two has yet to be explored. In an observational study, 50.5% women with nausea and vomiting in early pregnancy were found to have potential psychiatric problems.19 The severity of nausea and vomiting correlated independently with somatic symptoms, social dysfunction, anxiety, insomnia and severe depression.

Thrombosis The combination of pregnancy, dehydration, and associated immobility in a woman with hyperemesis increases the risk of venous thromboembolic disease.

Mallory–Weiss tears

Prolonged vomiting in hyperemesis patients predisposes to oesophageal trauma and Mallory–Weiss tears

Differential diagnosis for hyperemesis gravidarum

- Genitourinary Urinary tract
- Infection Gastrointestinal
- Gastritis Reflux oesophagitis
- Enteric infection
- Peptic ulceration
- Bowel obstruction
- Hepatitis
- Endocrine Diabetes Hyperthyroidism
- Addison's disease
- Hypercalcaemia
- Drug-induced vomiting
- Antibiotics
- Iron supplementation
- Other medication
- Neurovestibular disease
- Psychiatric illness

MANAGEMENT OF HYPEREMESIS GRAVIDARUM

Severe nausea and vomiting is a leading cause of hospitalization during pregnancy. It is estimated that the financial burden of hyperemesis is 200 million USD per year.2 Hyperemesis can be extremely debilitating for the patient and if inadequately managed can cause significant maternal morbidity. No single therapy has emerged as significantly beneficial because hyperemesis gravidarum is a syndrome with a multifactorial aetiology.31 In a systematic review, seven randomized controlled trials testing different methods of treatment in hyperemesis patients were identified, including oral ginger root extract, oral or injected corticosteroids or injected adrenocorticotrophic hormone (ACTH), intravenous diazepam, and acupuncture. treatments were shown to be of benefit. The management of hyperemesis is therefore based on correcting electrolyte imbalance and dehydration, prophylaxis against recognized complications, and providing symptomatic relief

Dietary and lifestyle

modifications Women suffering from hyperemesis may spontaneously change their diet and eating patterns. Small and frequent dry meals are usually more tolerable than fatty, fried and spicy food. Drinking small amounts of fluid regularly is important to maintain hydration. Eating before getting out of bed and at times when nausea is less severe may reduce the severity of nausea and vomiting. Women with hyperemesis may notice that they are sensitive to certain scents and learn to avoid them. All these modifications may help reduce symptoms, but in more severe cases are unlikely to provide sufficient protection from dehydration.

Intravenous fluid and electrolyte replacement

Maintaining hydration is crucial in managing hyperemesis. Women who are unable to tolerate oral fluids and who are ketotic should receive intravenous fluid and electrolyte replacement. This can be done in either an outpatient or an inpatient setting. Normal saline or Hartmann's solution are recommended to correct possible hyponatraemia. Potassium chloride can be added if necessary, according to the patient's serum sodium and potassium levels. The use of 2N saline potentially results in too rapid a correction of serum sodium level, even in severe hyponatraemia, and can lead to central pontine myelinolysis. Dextrose-containing fluids should also be avoided as Wernicke's encephalopathy may be precipitated by carbohydrate-rich food and intravenous dextrose.20

Thiamine (vitamin B1)

supplementation Thiamine requirement in pregnancy increases during pregnancy to 1.5 mg/day.20,26 Patients with prolonged vomiting should receive thiamine supplementation to prevent Wernicke's encephalopathy. Oral tablets can be given if tolerated. Alternatively, weekly intravenous preparations can be given as part of multivitamin infusion .

Pyridoxine (vitamin B6)

Two trials have suggested that pyridoxine is effective in reducing the severity of nausea in hyperemesis gravidarum, but there is no evidence of an effect on vomiting.1 This potentially reflects a dose response effect, with a higher dose showing greater effect in those with worse symptoms. Bendectin (Debendox) is a combination of doxylamine and pyridoxine, specifically designed for nausea and vomiting in pregnancy, which has been proven to have great efficacy. Unfortunately it was removed form the market in 1983 because of claims of teratogenicity which were subsequently proven to be unfounded.32,33 Bendectin is arguably the most effective medication for nausea and vomiting in pregnancy, with the best-known safety profile; paradoxically it is not available in most parts of the prescribing world. Hyperemesis gravidarum 763 A delayed-release combination of doxylamine/pyridoxine (Diclectin: 10 mg doxylamine, 10 mg pyridoxine) is the only approved antiemetic medication for use in pregnancy in Canada. An observational, prospective study involving 225 women with nausea and vomiting in pregnancy concluded that the standard dose of Diclectin, or higher dose calculated per kg of body weight, does not affect either the incidence of maternal adverse effects or pregnancy outcome. If needed, Diclectin can be given at doses higher than the standard four tablets a day to normalize for body weight or to optimize efficacy.

Antiemetics

In the majority of cases of hyperemesis, fluid and electrolyte replacement with vitamin supplementation is sufficient to elevate symptoms and prevent serious complications. When patients fail to respond to such supportive management, there is a place for antiemetic therapy. There is an understandable reluctance to prescribe or receive antiemetics after the post-thalidomide scare. More than 75% of women in one study believe antiemetics increase teratogenic risk, and led them to have an increased tendency to terminate their pregnancy due to misinformation and misperception.35 This perceived risk and propensity to terminate pregnancy decreased significantly after counselling. A systematic review has shown that antiemetics are more effective than placebo in reducing the frequency of nausea and vomiting in early pregnancy.1 There is extensive evidence to support both the safety and effectiveness of Bendectin/Diclectin (doxylamine, pyridoxine), antihistamine (H1 receptor antagonist) and phenothiazine use for nausea and

vomiting in pregnancy.32,33,36 A large Swedish population-based study looking at use of antiemetics (antihistamines, dopamine modulators, and ondansetron) in pregnancy reported that neonates born to women who used any of the antiemetics had a reduced risk for low birth weight, prematurity, being small-forgestational age, and congenital malformations.37 No specific differences were observed with respect to the outcome following a comparison of different antiemetic drugs. They concluded that women using antiemetics have a better pregnancy outcome than other women. This may reflect better nutritional status, or possibly this merely reflects the healthy placentation that is associated with nausea and vomiting in pregnancy. There were no signs of teratogenicity of the drugs studied.35,37 Therefore, persistent nausea and/or vomiting in pregnancy should be treated with regular antiemetics Drowsiness is a common side-effect of antiemetics, particularly phenothiazines. This side-effect is often perceived as beneficial, as sleep and rest are widely believed to be useful in the management of hyperemesis. Extrapyramidal effects and oculogyric crises have been reported in pregnancy with both metoclopromide and phenothiazines. Extrapyramidal effects are reversible with the discontinuation of medication, and oculogyric crises may be treated with antimuscarinic drugs.

Corticosteroids Corticosteroids

have been used effectively as antiemetics in oncology patients; consequently they have been introduced as treatment for nausea and vomiting in pregnancy. Several earlier studies reported successful outcomes with the use of corticosteroids in women with hyperemesis gravidarum. However, these studies were underpowered,39,40 and a recent randomized, placebo-controlled trial involving 126 women revealed that the addition of parenteral and oral corticosteroids to the treatment of hyperemesis had no adverse effect on pregnancy and neonatal outcome, but also no beneficial effect on the course of hyperemesis.41 Rates of resolution with placebo are high. In this study, rehospitalization for hyperemesis occurred in 34% of women who received corticosteroids compared with 35% of women who received placebo. The lack of a trend in the proportion of women rehospitalized in this study makes it unlikely that a larger sample size would reveal a significant benefit for corticosteroid therapy in reducing the number of remissions for hyperemesis gravidarum.

Psychosocial support

Most women with hyperemesis found the knowledge that nausea and vomiting is 'normal' and will regress as the pregnancy progresses reassuring on its own, and this should be a consistent part of their counselling. All patients with hyperemesis need reassurance, encouragement and emotional support on a regular basis. Psychotherapy and psychiatric intervention may work and in some cases may be necessary, but this should be tailored to patients' individual needs.

Medical termination of pregnancy

In rare circumstances when all forms of treatment fail or the maternal condition becomes life-threatening, termination of pregnancy is the only definitive cure.

RECURRENCE RISK OF HYPEREMESIS

The risk of recurrence of hyperemesis in subsequent pregnancies when it occurs in the first pregnancy is approximately 15.2%. Interestingly, this risk is reduced by a change of paternity. The risk of hyperemesis in the second pregnancy is increased with increasing time interval between deliveries, but only in women with no previous hyperemesis.49 Further studies are needed to explore the relative impact of genetic and environmental factors on hyperemesis gravidarum. Women with hyperemesis in her first pregnancy should be counselled of this fact

CONCLUSION

The pathophysiology of hyperemesis gravidarum is incompletely understood; consequently most commonly used treatments are empirical in nature and less than effective. The cornerstone of management is adequate fluid replacement and thiamine supplementation which will avoid life-threatening complications. The use of antiemetics is safe in pregnancy. Adverse perinatal outcome such as low birth weight, poor Apgar score and preterm delivery are mostly attributed to poor maternal weight gain rather than hyperemesis itself. Further research is clearly required; it may be beneficial to regard hyperemesis gravidarum as a 'syndrome' involving complex biological, psychological and sociocultural elements.

Summary

Nausea and vomiting are common in pregnancy and the condition may be mild or severe disabling disease. The severe form is known as HG which is characterized by dehydration, electrolyte and metabolic imbalances, and nutritional deficiencies that may cause hospital admission. The severity of NVP may be assessed by PUQE. Focused history and examination are needed to exclude the differential diagnosis. Moreover, lab investigations are useful tools to assess complications. Many theories have been hypothesized to contribute to the pathogenesis of HG. Hormones like estrogen, progesterone, hCG, and serotonin may play a role. Cytokines and fetal cell-free DNA are considered evidence for immunological etiology. A debate is found between researchers regarding psychological etiology because a causal relationship has not been established yet

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