Review

Hyperemesis gravidarum

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ABSTRACT

Hyperemesis gravidarum (HG) is defined as a severe form of Nausea and Vomiting of Pregnancy (NVP) and is characterized by nausea and excessive vomiting that can start as early as the 6th week of pregnancy, and last up to the middle of the second trimester. No definitive diagnostic criteria exist that could exactly differentiate HG from NVP, but in clinical practice loss of >5% of body mass as a result of vomiting and loss of appetite is considered a clear sign of the disorder. Pregnant women with HG can also have other gastrointestinal, metabolic and neurological symptoms, so it is important to rule out other possible causes of vomiting in pregnancy. Since the disorder is self-limiting, the primary aim of the treatment is to manage the symptoms and avoid possible complications due to hypovolemia and malnutrition. The therapeutic approach can be nonpharmacological in milder cases, but in severe cases, vitamin B6 (pyridoxine) in combination with doxylamine has proven to be the most effective therapy.

KEYWORDS: hyperemesis gravidarum; vomiting; nausea; pregnancy

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INTRODUCTION

Nausea and vomiting of pregnancy (NVP) are one of the most common disorders, reported in 70-80% of all pregnant women (1, 2). The symptoms usually occur during the first trimester, starting at the 5-6 week of gestation, peaking in the 9th week, and then stop around 20th week of gestation (2). Hyperemesis gravidarum (HG) is an extreme form of this disorder, characterized by severe nausea and vomiting, that affects 0.3-2% of all pregnant women (1, 3). Excessive vomiting can result in weight loss and hypovolemia, which can lead to metabolic disorders and issues both for the mother and the fetus.

EPIDEMIOLOGY

Epidemiologic studies have identified some common factors in women who have HG. Those are younger age, nulliparity, trophoblastic disease, history of motion sickness and migraines, female gender of the fetus and history of NVP in the maternal line. Smoking seems to be a protective factor due to its association with decreased concentrations of human chorionic gonadotropin (hCG) and estradiol (4, 5).

ETIOLOGY

In spite of the fact that NVT and HG are not rare in the population of pregnant women, both etiology and pathogenesis of these conditions remain

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unknown. There are a large number of theories that try to explain these disorders.

Genetic theories are based on studies that show an increased risk for NVP and HG among female relatives, and no change in severity of the disorder while switching partners, suggesting that paternal genes play at the most minor role in hyperemesis (6, 7). Studies have been made regarding 2 genes responsible for both placentation and appetite regulation during pregnancy (GDF15 and IGFBP7) and they have shown a positive correlation between expression of these genes and severity of NVP, what could be the key for the better understanding of these disorders in the future.

Placental factors are also potentially significant for it has been shown that in conditions where the volume of the placenta is decreased (older, multiparous women, smokers), there is less chance for NVP to occur (8).

There is a strong correlation between elevated hCG serum concentration and severity of NVP/HG, although the mechanism behind it is still unknown. Since hCG has a role in thyroid metabolism, elevated concentrations of hCG in NVP/HG are frequently followed with increased concentrations of thyroid hormones, T3 and T4. This condition can evolve into gestational transient thyrotoxicosis (9).

Although there are several different theories regarding the cause of HG, none of them completely explain the pathogenesis of this disorder so, for now, it is safest to say that this is a disease with a multifactorial background.

CLINICAL PRESENTATION

Despite the widely used term 'morning sickness', NVP/HG persist throughout the day in most cases and are limited to the morning in less than 2% of women (3, 10). HG is characterized by severe nausea and vomiting starting before the end of the 22nd week of gestation (WHO, 2016), and it interferes with liquid and food intake that can lead to dehydration, metabolic misbalance, nutritional deficiency, ketonuria and loss of more than 5% of body weight (1, 11). Women can also experience excess salivation, gastroesophageal reflux symptoms, elevated liver function tests and Wernicke's encephalopathy (1, 3, 12, 13). Differential diagnosis includes gastrointestinal diseases, such as gastroenteritis, GERD, peptic ulcer, pancreatitis, appendicitis, biliary disorders; genitourinary disorders like nephrolithiasis, pyelonephritis; metabolic, neurologic and pregnancy-related disorders (3). In order to diagnose NVP/HG, a clinician should rule out all of the disorders above, since there are no definitive diagnostic criteria for hyperemesis gravidarum. Laboratory tests include blood count (raised hematocrit, anaemia), liver function tests (AST and ALT levels are raised in up to 67% of cases), urinalysis (+ketonuria), electrolytes (hypokalemia, hyponatremia, low serum urea, high creatinine, metabolic alkalosis), thyroid function tests (high T4, low TSH in up to 66% women with HG), though none of these findings can serve as a definitive marker of the disorder (14). Way to partially objectify the severity of NVP/HG is through mother risk pregnancy-unique quantification of emesis and nausea (the PUQE index), that has proven to be a helpful clinical tool when deciding which approach to take regarding therapy and medication of NVT/HG (15). Besides the physical effect of HG, some women experience significant psychosocial morbidity caused by nausea and vomiting, ranging from higher depression and anxiety scores to decisions for pregnancy termination (16). Regarding effects of NVT/HG on the fetus, studies have shown a lower rate of miscarriage when compared with the control group, and no significant association of hyperemesis gravidarum with congenital anomalies (17).

THERAPY

Since NVT and HG are self-limiting conditions that usually end during the second trimester, the treatment is supportive. The goal is to manage the symptoms (nausea, vomiting, heartburn, and salivation), correct dehydration/hypovolemia and electrolyte abnormality and prevent complications of the disease (14). Depending on the severity of NVT, there are two possible treatment choices, nonpharmacologic therapy, and pharmacologic treatment. Nonpharmacologic therapy is suitable for milder cases of NVP (as evaluated by mother-risk PUQE index), and it includes dietary measures, emotional support, acupressure and ginger (3). New guidelines suggest that pharmacological treatment should be recommended after all the measures above have proven ineffective. First-line pharmacotherapy should include vitamin B6 (pyridoxine) alone or in combination with doxylamine (18). Dopamine antagonists (promethazine, metoclopramide), antihistamines (diphenhydramine), phenothiazines, H2 blockers, and PPI are also possible choices but only if the patients are unresponsive to the first-line pharmacologic therapy (14). Although ondansetron was found to be more effective than the first-line therapy, there is still additional research to be made on fetal safety while using this drug (19, 20). Corticosteroids should only be given in very severe

cases, and only if the other therapeutic options have failed because of the confirmed association between oral clefts and methylprednisolone use in the first trimester (21).

General supportive therapy, such as intravenous fluid replacement and enteral tube feeding should be initiated to all women with HG who cannot maintain their weight or have not been reacting to therapy. Also, dextrose, vitamins, and thiamin should be included when there is a long period of vomiting.

CONCLUSION

Although a large number of pregnant women suffer from NVT/HG, there is still very little scientific data regarding definitive etiology and pathophysiology of these disorders. Multifactorial background of the disease is almost certain, but for clinical practitioners, the key for proper treatment is defining diagnostic criteria, and that can only be done once we understand the mechanisms behind nausea and vomiting during pregnancy.

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