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RISK FACTORS OF HYPEREMESIS GRAVIDARUM: REVIEW ARTICLE

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ABSTRACT

Hyperemesis gravidarum (HG) is the most severe form of nausea and vomiting during pregnancy (NVP). It is diagnosed clinically by its typical clinical picture and exclusion of other causes of nausea and vomiting in the pregnant woman. Nausea and vomiting are a common experience affecting 50% to 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 to 2% of cases but when it occurs, it may be associated with morbidity of both mother and fetus. There are many risk factors related to HG, but we are still in need of adequate clinical research methodology and design for reporting these associations. In this article, we will discuss them and review epidemiological studies and statistics that support them. HG is found to be common in young aged mothers. There is a debate between studies regarding ethnicity as a risk factor. Low socio-economic level is found to be associated with HG. Dietary factors are considered in Indians who are mostly vegan and Asians who are mostly lactose intolerant. Deficiencies of trace elements are associated with more progression of the disease. Women affected by NVP are mostly nonsmokers. Molar pregnancy, multiple pregnancies, fetus with Down syndrome and primigravida are common obstetric risk factors. Studies theorize relation between hyperthyroidism and HG based on structural similarity between hCG and TSH but more studies are needed to highlight this relation. Mood and anxiety disorders are associated with the disease but causal relation has not been established yet. GERD, peptic ulcer disease and specifically *H. pylori* infection are among common risk factors. Asthma is associated with prolonged duration of hospitalization. Strong positive family history of HG in patients highlights genetic predisposition of this disease.

Keywords: Hyperemesis; Disease; Health.

KEYWORDS : NVP: Nausea and Vomiting in Pregnancy; HG: Hyperemesis Gravidarum.

INTRODUCTION

Nausea and vomiting is a common disease among pregnant women. The spectrum of nausea and vomiting range from mild to severe disease which involves persistent and excessive vomiting [1]. The severe form of the disease is hyperemesis gravidarum (HG) may cause significant maternal and fetal complications if not treated adequately [2].

The term "morning sickness" is a miss-nomination, as this condition often lasts throughout the day not only in the morning [3]. Only 17% of women suffer nausea only in the morning [4].

The International Statistical Classification of Disease and Related Health Problems, Tenth Revision, defines hyperemesis gravidarum (HG) as persistent and excessive vomiting starting before the end of the 22nd gestational week and further subdivides it into mild and severe, the severe condition is complicated by metabolic disturbances such as carbohydrate depletion, dehydration or electrolyte imbalances [5].

The incidence of NVP reaches 91% which equals approximately 4 million and 350,000 women who are affected every year in the United States and Canada respectively [2]. Although HG is a rare disease compared to NVP, it occurs in 0.3% to 2% of all pregnancies [6]. It varies with ethnicity and ranges between 3 and 20 per 1000 pregnancies [2,6]. This varies may be due to different diagnostic criteria in addition to ethnic variation in populations [7]. NVP is found more often in Western countries and urban populations and is rare among African societies, Native Americans, Eskimos, and most Asian populations. A study from Canada of 367 women found that Asians and blacks were less likely to report symptoms of NVP than Caucasians. Socio-demographic factors did not explain the racial/ethnic variation in disease prevalence, suggesting that genetic and/or cultural factors may contribute [2].

Its severity can be assessed using the Pregnancy Unique-Quantification of Emesis (PUQE) Score which has been validated and has an intimate correlation with clinical diagnosis and severity of the case. The PUQE score includes questions on the number of daily vomiting episodes, the length of nausea per day in

hours and the number of retching episodes, with a minimum score of 3 and a maximum score 15. A score of <6 suggests mild HG, 7-12 is moderate HG and 13 or more is a severe disease [8].

The PUQE score is also used to monitor treatment outcome during hospitalization on daily basis [8]. The score of PUQE is found to be related to the quality of patient's life and her willing to be pregnant again [9]. Moreover, a strong inverse correlation between the scores of the PUQE questionnaire and the self-reported food intake and weight gain [10].

Risk Factors

There are many risk factors related to HG, but we are still in need of adequate clinical research methodology and design in reporting these associations [11].

Personal risk factors

Age: Most studies agreed that hyperemesis gravidarum is more common among young aged mothers [12,13]. Moreover, young age of pregnant women also carries a risk of prolonged duration of the disease more than 27 gestational weeks [14,15]. The decreased risk of incidence of hyperemesis with age may be explained by subsequent dealing with high estrogen levels by the production of sex hormones binding globulin during subsequent menstrual cycles [16].

Socioeconomic factors: The low socioeconomic level is considered as a risk factor to HG [14,15,17,18]. But socio- demographic factors did not account for the racial/ethnic variation in prevalence of HG, but these variations among societies are due to other cultural, genetic and diet-related factors [2]. Low socio-economic living is also a major risk factor for infection with *H. pylori*, that is why Infection with *H. pylori* should be kept in mind in cases of HG in pregnant women with lower socioeconomic status because crowded populations which are mostly characterized by poverty, have an increased risk of transmission and higher prevalence rates of *H. pylori* [17] because *H. pylori* is thought to spread between persons through the fecal-oral or oral-oral route and contaminated water is a possible environmental reservoir [19]. It was interested to find that women who worked outside home have lower risk of HG and NVP compared with housewives [13]. It was found that the biological

relationship between partners which are common in many societies especially in Africa and the Middle East is not associated with an increased woman's risk of developing HG [20].

Dietary factors: Researchers studied the diet of pregnant women during the 12 months preconceptionally and they found that women with certain dietary habits are at risk of HG in different populations e.g., Asian, Indian people [21]. Asian women have an increased risk of HG due to being lactose intolerant and have diets low or deficient in dairy products [14,15]. Indian population who are more commonly to be vegan, are more likely to have HG [14,15]. This data could be used for the development of new strategies in the management plan of HG [22].

It is also found that pregnant with high fat intake is more liable to HG [23] restrictive pre-conceptional diet like vegan diet or high BMI diet also carries the risk of prolonged duration of the disease [14,15]. On the other hand, a high intake of fish and seafood and a high intake of allium vegetables have a reduced risk of developing HG. Interestingly, The intake of one to two glasses of water daily seemed also to be protective against HG [21]. Deficiencies of trace elements and vitamins either due to diet or repeated vomiting have been considered as possible etiologies of progression to hyperemesis gravidarum [12]. So recommendations about weight control should be given to women with high or low BMI preconceptionally [22].

Smoking: It was found that women who vomit in pregnancy are less likely to be smoker [18] and this relation is considered preexisting and it is not a response to either the pregnancy or the vomiting [16]. It may be explained as smoking pregnant women also have lower levels of estrogen and there is a relationship between high estrogen level and HG [16]. If NVP is an expression of a well-functioning placenta, the negative relation with smoking may be because of a negative effect of maternal smoking on early placental development during embryogenesis [13].

Obstetric factors

The incidence of HG is higher in multiple pregnancy [18], molar disease and Down syndrome [24]. Nulliparous has higher risk because of having higher serum [18] and urinary estrogen levels than multiparous women and those women in their first pregnancies have higher first-trimester estrogen levels than in subsequent pregnancies [16]. The risk of hyperemesis in the second pregnancy increased with increasing time interval between pregnancies [25]. In multiple pregnancies, it was found that the incidence of HG is higher in male-male twins and male-female twins, all female twins have lower incidence which was unexpected because of higher maternal estrogen levels [18]. Although, it has been well established that patients with hyperemesis have altered sex ratios and her fetus is mostly a female and maternal levels of hormones associated with female fetus may play a role in the pathogenesis of disease [18]. Also it was found that having singleton female fetus is associated with higher incidence of hospitalization in HG [14,15,17,18].

Medical factors

Hyperthyroidism: Diagnosis of thyroid disease and interpretation of thyroid function tests in women is complex in pregnancy as there are different ranges which vary from one trimester to another because of structural and functional similarity between TSH and hCG [12]. Although autoimmune thyroid disease has previously been considered the most common cause of thyrotoxicosis in pregnancy [26], recent studies indicate that increased production of hCG is the most common cause of abnormal thyroid function tests at the first trimester of pregnancy [27]. And it was found that pregnant women with past medical history hyperthyroidism are more liable to HG at their pregnancy [18].

In fact, decreased thyroid stimulating hormone has been found in HG patients with normal levels of free T3 and free T4 [1]. So it is thought that there may be a condition known as transient hyperthyroidism of hyperemesis gravidarum (THHG) [12], which is a self-limiting hyperthyroidism co-exist with HG. Diagnosis of THHG is based on the following criteria:

Abnormal thyroid function tests coexist with hyperemesis gravidarum.

No past history of hyperthyroidism

Absence of physical examination findings that indicate hyperthyroidism

Negative thyroid antibodies panel [24].

It has been suggested that the high incidence of transient hyperthyroidism in HG patients is caused by high levels of circulating hCG and hypersensitivity of thyroid hormone receptors for hCG or the presence of a certain type of hCG that is more effective in stimulating the thyroid gland. During peak hCG levels in normal pregnancy, serum TSH levels decrease and free T3 and T4 levels are significantly elevated at this time induced by hCG which mimics TSH in stimulating the thyroid gland. That's why hCG has a role in causing hyperthyroidism and this is supported by thyroid hyper-stimulation in cases of molar and multiple pregnancies, diseases that are associated with higher hCG levels [24].

Indeed, classes of hypersensitive TSH receptors have been observed in certain cases with gestational hyperthyroidism and HG. Those patients who suffered from recurrent HG during pregnancies with hCG levels within the normal range were found to have a mutation in the extracellular domain of the TSH receptor that made it over responsive to normal serum hCG levels [28].

As women with hyperthyroidism uncommonly complain of vomiting, it may be unlikely that thyrotoxicosis or abnormal thyroid functions are the main cause of hyperemesis gravidarum [12]. Evidence supports a relationship between hCG levels and THHG, but the exact role in HG is still in need to be studied. Whether hCG level can participate in the triggering of vomiting or vomiting is a parallel coexistence of hypersecretion of hCG. In addition, hyperthyroidism is more prevalent but not only occurs in those patients, and many other HG patients do not suffer from hyperthyroidism [24].

Mental health problems: Pregnant women with past medical history of depression, anxiety or any mood disorder are more liable to HG at their pregnancy [18]. Moreover, stress and marital conflicts have been associated with increased risk of HG [1]. A significantly high incidence of depression and anxiety occur in women with HG especially with prolonged duration of the disease which makes it difficult to explain the causal relation between HG and mental health problems [29].

Providers should immediately manage women with HG by including the psychological care and support [30]. Moreover, managing women with HG requires the health care providers to understand that patients' quality of life is severely disturbed while they are supposed to be happy for having a new baby, especially in primigravida. Patients complain that their health care providers can not realize how ill they are. They may be depressed just as any patient experiencing disabling disease can so our role as a physician is to normalize the patient's sense of anxiety because of the disease and counsel about any negative thoughts about her condition or her fetus [31].

GIT disorders: There is a correlation between hormonal level

changes in pregnancy especially high progesterone level and relaxation of the upper esophageal sphincter and other GIT sphincters; this may have a role in pathogenesis dyspepsia of pregnancy [12]. Pregnant women with past medical history of peptic ulcer and GERD are more susceptible to hospitalization due to HG [18]. Recently, *Helicobacter pylori* infection has been implicated as a possible cause of HG. In a prospective study, *Helicobacter* serum IgG concentrations in patients with HG were compared with those in asymptomatic pregnant women of the same gestational week. Positive IgG concentrations were found in 95/105 hyperemesis patients compared with 60/129 control patients. The authors conclude that there is an association between infection with *H. pylori* and HG [1]. This was also confirmed by El Younis et al. [32] who treated two pregnant with HG by erythromycin; all the symptoms resolved via this treatment.

A question that needs to be answered is whether an increased incidence of nausea and vomiting may lead to the elevated levels of *H. pylori* found in these pregnant patients due to loss of acid and creation of basic environment favors *H. pylori*'s growth [1]. Another possible explanation is that a displacement of intracellular and extracellular volume occurs in early pregnancy as a result of the increase in steroid hormones, and these results in a change of pH which could favor *H. pylori* infection [17]. Although an association between hyperemesis gravidarum and *H. pylori* infection is suggested, the considerable heterogeneity among studies cause limitations of these studies [19]. Moreover, we need specific guidelines for diagnosis and treatment of *H. pylori* during pregnancy have not been established yet [19].

Respiratory disorder and allergies: Pregnant women with past medical history of asthma and other respiratory disorders were found to be more liable to hospitalization due to HG [18]. Besides, Past history of allergy has been associated with prolonged duration of the disease [14,15]. Autoimmune theory for HG and its response to steroid in certain refractory cases may support this association [14,15].

Genetic factors: One of the theories that try to explain the etiology of hyperemesis gravidarum is the presence of a genetic role. A 2008 study by Fejzo et al. in California, USA included 1,224 patients with hyperemesis gravidarum and showed the significance of positive family history in the development of the disease. In this study, 28% of patients were found to have a family history of hyperemesis gravidarum in their mothers, 19% reported a sibling with hyperemesis gravidarum and 9% of the patients reported at least 2 biological relatives with this disease. Interestingly among the most refractory cases, those requiring total parenteral nutrition (TPN) or nasogastric feeding, the percentage of patients with affected sisters was 25% [7].

CONCLUSION

Many risk factors are involved in the pathogenesis of HG. HG is found to be common in young aged mothers. A conflict between studies was found regarding ethnicity, but low socio-economic level is found to be associated with it. Dietary factors are common in Indians who are mostly vegan and Asians who are mostly lactose intolerant. Deficiencies of trace elements are associated with progression of the disease. Women affected by NVP are mostly nonsmoker. Molar pregnancy, multiple pregnancies, fetus with Down syndrome and prime-gravidity are common obstetric factors of HG. Studies theorize the relation between hyperthyroidism and HG based on the structural and functional similarity between

hCG and TSH but more studies are needed to highlight this relation. Mood and anxiety disorders are associated with the disease but causal relation has not been established yet. GERD, peptic ulcer disease and specifically *H. pylori* infection are among common risk factors. Asthma is associated with prolonged duration of hospitalization. Strong positive family history of HG in patients highlights the genetic predisposition of those patients.

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