Original Research

Factors associated with hyperemesis gravidarum

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Summary

Introduction: Nausea and Vomiting of Pregnancy (NVP) is a common health condition during pregnancy, often referred to as 'morning sickness'. The most severe degree is Hyperemesis Gravidarum (HG). The reasons for this phenomenon are still somewhat unclear. *Methods*: The sample included 201 fertility-age women, who had experienced at least one pregnancy. Data were gathered by a questionnaire that included sociodemographic questions and validated questionnaires: BSI, anxiety state and anxiety trait. *Results*: A relationship was found between existing gastrointestinal disorders and HG, and anxiety state and HG. Logistic regression significantly showed that previous gastrointestinal disorders predicted HG. *Discussion*: It seems that the emotional state and physical condition are related to HG, and that women with gastrointestinal diseases are more likely to suffer from HG.

Key words: Hyperemesis Gravidarum (HG); Nausea and Vomiting of Pregnancy (NVP); Somatization; Anxiety.

Introduction

Nausea and vomiting during pregnancy (NVP) characterize a common health condition (provided it is not related to an organic factor). 70-85% of pregnant women suffer from the phenomenon, generally referred to as 'morning sickness'. NVP is common during the first trimester, peaks at about 10-16 weeks, and in 90% of the cases – passes by week 20 [1]. The symptoms vary greatly among pregnant women. The classification method of NVP refers to its effect on the pregnant woman's life: light, medium or severe [2]. Persistent and excess vomiting during pregnancy – hyperemesis gravidarum (HG) – is different from morning sickness and is considered the most severe level of NVP. Hyperemesis is defined as more than three vomiting sessions per day, 5% weight loss or three kilograms of the woman's initial weight, and the presence of ketones in the urine. The phenomenon lasts throughout the pregnancy and can cause dehydration and damage to the mother and the fetus [3]. Excess vomiting during pregnancy can cause problems in fluids and electrolytes stability and acid-base balance, as well as nutrition deficiencies. It also affects the fetus' birth weight and can increase the risk of miscarriage [1, 4]. The condition requires hospitalization, and its frequency in the population is 0.5-2%.

The factors and mechanisms of HG are still unclear. Few studies were conducted to identify the etiology, features, complications and treatment of HG [5].

Studies have indicated additional factors that could affect morning sickness. Some claim that it is related to a genetic disposition; namely, if a pregnant mother experienced HG, it is highly likely that her daughter, when pregnant, would experience it too, so there may be a genetic effect [6,7]. It has also been stated that carrying a female fetus could be a risk factor for HG, and that the occurrence of HG in a first pregnancy would increase the risk of HG in future pregnancies [7]. Others have indicated that a high hormone level during pregnancy could slow down digestion processes, which could cause disorders such as heartburn, reflux, nausea and vomiting [8].

It has been shown that HG is more prevalent among women, who suffer from diseases such as diabetes, hyperthyroidism or hypothyroidism, gastrointestinal tract disorders, a history of molar pregnancy, and psychiatric illness before they became pregnant [9]. Studies, which addressed the relationship between HG and mental distress during and after pregnancy, found a possible link between nausea and vomiting and psychological factors such as psychiatric illness, depression and anxiety [1, 10-13].

Other studies linked the HG phenomenon to a variety of factors such as the sex of the fetus, the number of fetuses, the mother's previous illnesses, illnesses that developed during pregnancy, hormonal problems, and more [8].

As mentioned, the factors and mechanisms of HG are still unclear. Few studies were conducted to identify the etiology, features, complications and treatment of HG [5].

The last decade of medical literature supports new theories about the causes of NVP. Scholars agree that the condition is driven by a combination of a number of factors: physiological, mental, economic, socio-cultural, hereditary, etc. Research findings showed that women in the test group (who suffered from HG) had a 60% chance of having elevated levels of HCG, compared to 9% in the control group. HCG was found to irritate the thyroid. The findings proved that the degree of hyperthyroidism was directly affected by the increase of HCG. In addition, the degree of chemical hyperthyroidism and level of HCG changed directly with the severity of vomiting [14]. In addition, a high frequency of helicobacter pylori – a gastrointestinal bacterium – was found among women suffering from HG

[9, 15]. Pregnant women, who received anti-bacterial treatment, suffered less from the HG phenomenon. The bacterium as a cause of the condition could explain the difference in the HG frequency among various ethnic groups. However, pregnant women with a helicobacter pylori infection are still not symptomatic.

Furthermore, the pathogenesis of HG is related to disturbances in the gastrointestinal system's mobility, characterized by reversed flow from the duodenum to the stomach and esophagus, resulting in nausea and vomiting. Another theory suggests that HG is related to lack of vitamins such as B6 (pyridoxine) and zinc, but there is no concrete proof of this link [16]. Controlled studies have shown that Doxylamine (an antihistamine) combined with vitamin B6 reduces about 70% of nausea and vomiting in pregnancy [17].

Many studies emphasized the relationship between HG and the woman's mental state. A link was found between HG and depression, but the direction of the link remains unclear. It was found that the longer the woman suffers a depression episode, the more likely she is to experience HG during pregnancy [18]. The prevalence of major depression generalized anxiety disorder, avoidant personality disorder and obsessive-compulsive personality disorder has been shown to be higher in women with HG [19].

Due to the lack of uniform guidelines many physicians find it difficult to treat patients. Research of the frequency of HG has led to the recommendation that doctors and nurses should pay more attention to pregnant women diagnosed with HG, to identify the causes, and to administer appropriate treatment [1, 20].

In view of the above, and because the pathophysiology of HG is still unclear, this study aimed to examine the factors that could predict the condition, and the link between them and HG.

The following hypotheses were examined:

H1: A relationship will be found between sociodemographic data, anxiety state, anxiety trait and somatization and the frequency of the HG phenomenon.

H2: Differences will be found between women who suffered nausea and vomiting up to week 20 and women who suffered beyond week 20 in all sociodemographic and personality variables.

H3: Background and sociodemographic variables and personality characteristics will predict the frequency of the HG phenomenon.

The importance of this research and its expected benefits are: Knowledge about the contribution of sociodemographic factors and personality traits to the phenomenon of HG in pregnancy may contribute toward understanding how to improve the wellbeing of these women, and to provide medical practitioners with guidelines for effective care that would promote their health. Analysis of this study's results could serve as a base of knowledge to build a training program for easing HG symptoms by using innovative methods in clinical practice.

Methods

This quantitative-correlative study was approved by the Ethics Committee of Ruppin Academic Center (2018-19/L/ND) and all participants provided written informed consent. The dependent variable is the HG phenomenon. The independent variables are BMI (body mass index), age, background illnesses, and personality characteristics: anxiety state, anxiety trait, and somatization.

Participants

Data were obtained from 201 women, who answered an online questionnaire.

The questionnaire was built through Google Forms, which helped to follow the reply rate online. Participants were recruited through social networks (Instagram, Facebook) or online forums of mothers and/or pregnancy. The criteria to participate in the study were that the woman is of fertility age, and has been pregnant at least once or is currently pregnant. The women answered the questionnaire after having signed a consent form.

Tools

The questionnaire was divided into a number of sections:

a) Background and sociodemographic data (adapted to the research)

b) Anxiety trait: This questionnaire examines anxiety as a personality trait, relates to the subject's regular emotional state, and represents the potential to develop anxiety state [21]. It includes 19 items on a Likert scale of 1 to 4; Cronbach's $\alpha = 0.678$.

c) Anxiety state: This is the second part of the anxiety trait questionnaire [21] that includes 17 items. It examines the subject's current state of anxiety, usually following an anxiety-enhancing event. The subject rates her feelings that day on a Likert scale of 1 to 4; Cronbach's $\alpha = 0.878$. This study used the Hebrew version of the questionnaire [22].

d) BSI - Brief Symptom Inventory: This section assessed the perception of the problem by means of the short version of the Derogatis & Melisaratos, 1983 questionnaire [23]. – 13 items that describe various complaints or symptoms, some relating to pain (headache, lower back, chest pains, etc.) and others to unpleasant bodily sensations (stress, paresthesia, congestion, vomiting and dizziness). The subjects were asked to rate the frequency of these symptoms during the previous month. The questionnaire is suitable for clinical and non-clinical populations; Cronbach's $\alpha = 0.850$. The questionnaire was translated into Hebrew and has high inner validity and consistency [24].

Data Analysis and Results

Chi-square analyses were conducted to examine the relationship between the sociodemographic ad psychological variables and the frequency of the HG phenomenon. T-tests for independent samples were conducted to examine the differences between the various variables in the group that suf-

fered from HG up to week 20 and the group that suffered from HG beyond week 20. Logistic regression was performed to examine the effect of the independent variables on the dependent variable (HG).

Table 1 presents the distribution of the research population by background and personality traits.

To examine the first hypothesis (H1) – that a relationship would be found between sociodemographic data, anxiety state, anxiety trait and somatization and the frequency of the HG phenomenon – we conducted a Pearson's chi-squared test, and found a significant relationship between the level of anxiety state and the frequency of HG (r = 0.321; P = 0.02), and a significant relationship between a background of gastrointestinal tract disorders and the frequency of HG (χ^2 = 5.699; Cramer's V = 0.209; P < 0.05). No significant relationship was found between anxiety state, BSI, BMI, age, number of pregnancies, and number of births. Hence, H1 was only partly supported.

To examine the second hypothesis (H2) – that differences would be found between women who suffered nausea and vomiting up to week 20 and women who suffered beyond week 20 in all sociodemographic and personality variables – we performed a *t*-test for independent samples. To aid this, we constructed a dummy variable indicating a timeline of nausea and vomiting: 0 = nausea and vomiting up to week 20; 1 = nausea and vomiting beyond week 20. Table 2 describes the distribution of nausea and vomiting reports by weeks of pregnancy. The independent variables that were examined were: anxiety state, anxiety trait, BSI, BMI, age, number of pregnancies, and number of births. A significant difference between the groups was found for anxiety trait (t = 0.348, P = 0.03), so that women who suffered from HG beyond week 20 exhibited a higher level of anxiety trait. No significant differences were found between the groups for age, number of pregnancies, number of births, BMI, BSI, and anxiety state. Therefore, H2 was partially substantiated.

To examine the third hypothesis (H3) – that background and sociodemographic variables and personality characteristics would predict the frequency of HG – we performed logistic regressions on the dependent variable (HG), and found that only the variable 'gastrointestinal tract disorders' was significant (P < 0.05). Again, H3 was only partially supported.

Discussion

The present study examined the frequency of Hyperemesis gravidarum (HG) among 201 fertility-age women, who had experienced at least one pregnancy. The frequency of the phenomenon was examined vis-à-vis factors that had been previously examined in the relevant literature. We examined the relationships, differences and effects of anxiety state, anxiety trait, BSI, age, BMI, number of past pregnancies and births, and the existence of prior medical conditions.

We found a significant link between *anxiety state* and the frequency of HG, as well as between a background of *gastrointestinal tract disorders* and the frequency of HG, although no significant relationships were found with the other independent variables. Similar results were previously found that indicated that anxiety and depression were common in HG women when assessed at their first hospitalization with caseness rates of 46.9% and 47.8% respectively [5]. A longitudinal study of Chinese women in Hong Kong indicated that these rates compared unfavorably with anxiety and depression rates of 36.3% and 22.1% in the first pregnancy trimester, 32.3% and 18.9% in the second trimester, and 35.8% and 21.6% in the third trimester [11]. Anxiety and stress in HG are probably in the causal pathway of HG as a response to its deleterious physical effects. The psychological distress appears to be self-limiting in tandem with symptoms of HG [3]. Koot and colleagues (2017)[25] examined physical data in an attempt to predict whether BMI affected the HG phenomenon, but found no significant proof. However, they did show that suffering from HG would affect the pregnant woman's BMI, whether by gaining very little weight or no weight at all during pregnancy.

We also found a significant difference between women who suffered from HG up to week 20 and beyond week 20 for *anxiety trait*, so that women who suffered from HG beyond week 20 exhibited a higher level of anxiety trait. Previous studies have indicated a link between NVP and the pregnant woman's mental condition. Kjeldgaard *et al.* (2017) [18] found that women who experienced depression at any stage before pregnancy were more likely to suffer from nausea and vomiting during pregnancy. In another study that examined the relationship between HG and the likelihood to experience mental distress, it was found that HG women were more likely to experience mental distress (during pregnancy and even after having given birth) than women who had not suffered from HG [11]. Another study that linked the NVP phenomenon with the pregnant woman's mental condition found that her level of anxiety could cause the phenomenon [26]. Contrary to our findings, a different study found a link between the level of somatization and the HG phenomenon, so that the higher the level of somatization – the more frequent the HG phenomenon is. The argument was that when there is psychological stress, which is not properly treated, the woman could develop physical stress without physiological tests findings [27].

In this study, gastrointestinal tract disorders were found to significantly predict the frequency of HG. There is a relationship between HG and the existence of gastrointestinal diseases, which indicates that women who suffered from gastrointestinal disorders were more likely to suffer from HG during pregnancy. These findings are supported by previous studies, which examined the effect of certain gastrointestinal diseases on the likelihood of HG. One gastrointestinal disease reported by a number of patients was an infection caused by the helicobacter pylori bacterium, which is typically located in the deep layers of the gastric mucosa or duodenum, and weakens its resistance to its acidic environ-

Table 1. — *Research population distribution by background and personality traits*

Variable	Mean	SD	SD error
Anxiety state	2.6208	0.35113	0.04424
Anxiety trait	2.432	0.36493	0.03107
BSI	0.829	0.63625	0.05416
BMI	27.0669	12.18856	1.03756
Age	32.75	0.936	0.08
Number of previous pregnancies	2.937	0.9482	0.1195
Number of previous births	1.88	1.07	0.091

Table 2. — *Distribution of nausea and vomiting reports by weeks of pregnancy*

Pregnancy timeline	Frequency	%	Valid %
Up to 20 weeks	80	39.8	61.5
Beyond 20 weeks	50	24.9	38.5
Total responses	130	64.7	100
No response	71	35.3	
Total responses + non-responses	201	100	

ment. The bacterium attaches itself to the gastric epithelium cells and creates an inflammatory reaction that damages the surrounding cells, and can even cause a peptic ulcer. It has been indicated that infection caused by helicobacter pylori is clear evidence of the link between gastrointestinal diseases and the likelihood of HG [15].

The gastrointestinal tract undergoes dramatic modifications during pregnancy. Heartburn, nausea, abdominal cramps, and altered bowel habits are the most common gastrointestinal symptoms of pregnant women. However, it may be a challenge to distinguish among functional symptoms and the onset of diseases that require immediate medical attention. Significant advances were made in recent years to ascertain the outcomes and the best therapy in pregnant women with inflammatory bowel disease. As a result, it is now recommended to continue the immunosuppressants and immuno-modulators maximizing the mother's health throughout gestation [28].

In summary, it seems that the pathogenesis of HG is multifactorial, and involves a number of factors that affect the phenomenon.

Limitations

This study has a number of limitations. In order to examine the severity of excessive nausea and vomiting in pregnancy as HG, there is a need to collect data about the hospitalization history during the pregnancy. This detail could probably testify to the existence of the phenomenon and provide the possibility to examine other factors that could affect HG.

Since there is no uniform definition of the time dimension of HG, we had to define it after the data were gathered. We divided the women into two groups according to their pregnancy weeks, similar to other research of the phenomenon, which argue that vomiting after week 20 is con-

sidered excessive and not within normal limits (of NVP). Although this definition is supported by many studies, it is inconclusive.

Finally, we did not address other factors that might affect HG. Due to this study's nature – we could not examine physiological data and detailed medical history such as HCG levels during pregnancy, course of pregnancy, and detailed medical history. These issues should be investigated further.

Conclusions

It is obvious that HG is a rather widespread phenomenon, the causes of which are not conclusively clear. We examined a large number of factors that could affect the phenomenon, but could find only a few links. A relationship was found between anxiety state and HG, and between gastrointestinal disorders and HG, which could indicate the likelihood that women who suffer from gastrointestinal problems and are anxiety-prone would suffer from HG during their pregnancy.

We recommend that future research focuses on the woman's medical history with emphasis on the number of hospitalization days due to HG, which could reflect its severity.

Acknowledgments

Conflict of Interest

The authors declare no competing interests.

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