Research Article ISSN: 2833-0382

International Journal of Family Medicine & Healthcare

Helping Providers Better Understand Hyperemesis Gravidarum

Merhavy CE, Dietz GI and Merhavy ZI*

Ross University School of Medicine, Bridgetown, Barbados.

***Correspondence:**
Zachary I. Merhavy, Ross University School of Medicine, Bridgetown, Barbados.

Received: 10 Dec 2023; **Accepted:** 12 Jan 2024; **Published:** 19 Jan 2024

Citation: Merhavy CE, Dietz GI, Merhavy ZI. Helping Providers Better Understand Hyperemesis Gravidarum. Int J Family Med Healthcare. 2024; 3(1): 1-6.

ABSTRACT

Hyperemesis Gravidarum (HG) effects on average 0.3-3.3% of expecting mothers during pregnancy. The exact percentage of effected individuals may vary per study, as the reporting of HG can be inconsistent amongst providers due to a number of variables. The effect of this disease on patients as well as the lack of education and/or resources available to them presents a significant gap in medical treatment that is failing these vulnerable patients. Until recently, the etiology of the condition was not well understood, however, recent advances suggest the placentally expressed nausea and vomiting hormone GDF15 plays a major role. Due to lack of research into the subject, the knowledge available for safe and affordable pharmaceutical interventions and treatments is significantly lacking for these vulnerable patients. The combination of low prevalence only recently established diagnostic definition, and little clinical knowledge surrounding HG, impacts the resources and support that patients will receive. The severity of the disease often leads to deterioration of the physical, mental, and social health of patients. It is this lack of support and education that conveys the need for healthcare providers to be more knowledgeable about the disease, available treatment options, and offer compassion and support to these patients.

Introduction

Hyperemesis Gravidarum (HG) has been predicted to occur in approximately 0.3-3% pregnancies [1,5,6]. HG is classified as the most extreme form of nausea and vomiting experienced during pregnancy, ranking as the second leading cause of hospitalization among pregnant individuals [5,6]. Classical clinical presentation includes severe vomiting (often associated with dehydration), maternal weight loss, ketonuria, nutritional deficiencies, electrolyte disturbances, and/or low birth weight [5]. Although this diagnosis afflicts a small population of pregnant individuals, the lack of education and affordable services (i.e. IV home treatments), available to those that suffer from this disease has created a significant deficiency in quality of care that is failing these patients. This condition not only affects the physical health of mother and fetus, but also the mental state of the mother, and has been associated with long-term maternal consequences including anxiety, depression, and post-traumatic stress disorder, and suicidal ideation [7,16]. HG severely impacts each element of the biopsychosocial model of health through its strain on the mothers' body and mind as well as the social isolation and monetary cost of the disease [8]. Currently, research of HG is difficult to conduct as most studies either require being specifically designed for pregnant women, or these individuals are excluded from research trials as they do not meet the inclusion criteria to be researched [9].

The aim of this paper is to explore the current literature on the condition of HG regarding the cause, health impact, and available treatments in order to draw the attention of the need for further research and education on this condition to better support patients and their providers in navigating this diagnosis.

Epidemiology

Up to 90% of pregnant females experience nausea during pregnancy, and this nausea is accompanied by vomiting in 28-52% of this population [3]. Nausea and vomiting during pregnancy (NVP) typically resolve by the end of the first trimester, while those affected by HG may have persistent intractable vomiting

throughout all three trimesters leading up to birth [3,4]. There is some research that indicates HG is diagnosed higher among women of Asian and Middle Eastern ethnicities. Whether this is due to a true higher prevalence rate, or due to lack of formal diagnostic criteria is still unclear [4]. Pregnant individuals with a previous HG pregnancy, a GDF15 mutation, and a family history of HG are at the highest risk for this condition [17].

HG may only affect up to 3% of the world's pregnant population [1,5,6]. This small percentage may explain why many providers and healthcare professionals are unfamiliar with the condition and treatment methods currently available for patients suffering from HG, however, as it is the leading cause of hospitalization in early pregnancy, and second leading cause after preterm birth, this gap in knowledge is inexcusable [3,17]. Reported data shows certain trends in women that are diagnosed with HG (as previously mentioned), and with this progress in the etiology of disease there is potential to aid in identification and prevention of future symptoms [17]. Many research studies have been conducted in western countries, including the United States, Sweden, Norway, and other European countries, yet there is limited published research in other regions of the world; therefore, identifying HG incidence per geographic population is inadequate [3]. Research shows that women with HG have a higher prevalence of depression than control groups experience by almost 43% and require more time off from work by 51% [8]. In a study completed in 2011, among 377 participants with HG, based on the PTSD diagnostic three categories, 18% met the full criteria for posttraumatic stress symptoms (PTSS) [10]. Therefore, it is imperative that providers are better equipped with a deep understanding of HG to provide their patients with the best overall care.

Patient Experience

In 2021, an international consensus officially provided a definition of HG; symptoms begin before 16 weeks of gestation, severe nausea and vomiting, inability to eat or drink normally, and limit of daily activity due to disease [18]. A study published in 1987 expresses the need for a set diagnostic criterion of HG, citing the variability in diagnosis between hospitals treating expectant mothers experiencing similar symptoms [11]. This study was not the first to state this, however, the first definition was not established until 34 years later, poignantly illustrating how overlooked this condition and these patients have been. Currently, there is still no reliable treatment regimen, however, the reported prevalence of the disease is consistent, and patients continue to express dissatisfaction with the management of their care [4,5].

In a cross-sectional study of 107 women completed in 2019, a majority reported a lack of support from healthcare professionals and suboptimal management in their care [1]. This dissatisfaction likely stems from a lack of understanding of the illness by the provider and a perceived lack of empathy in the hardships these mothers undergo [1,8]. Reasonably, due to the deficit in provider education, understanding, and support, there are many adverse health and emotional effects that can lead to a variety of unfortunate consequences, including consideration of abortion, poor maternal health, suicidal ideation and/or poor fetal health [1,8,16]. Affected patients have described their HG pregnancies as "inhumane torture", or "9 months of torture", with 8 of 107 mothers seeking elective pregnancy termination and others requiring leaves of absence (to varying degrees) from work during the duration of pregnancy [1].

Severe physical and psychosocial impacts have been reported from patients that have experienced HG, whereas many patients have described symptoms of PTSS, and research supports an elevated biological risk of HG in future pregnancies, there is no psychosomatic cause of the condition established [4,19]. While the psychological trauma experienced in previous HG pregnancies may take a significant toll on the mothers and their perception of future gestations, there is no evidence of a psychosomatic influence in recurrence of HG in future pregnancies [4,19]. In the study completed by Havnen et al., mothers reported a repeating theme in their general practitioner care; a lack of understanding and support paired with insensitive or hurtful remarks from the physicians charged with their care, as well as a feeling that their physicians had a lack of knowledge or willingness to understand the impact on quality of life that this illness takes [1].

Adverse Maternal and Child Outcomes

Due to the severe vomiting that Hyperemesis Gravidarum patients experience they can suffer from various adverse symptoms and conditions, relating not only to the loss of nutrient intake but the act of vomiting itself over twenty times a day [16]. HG patients can develop Mallory-Weiss tears, pneumothorax, pneumomediastinum and retinal detachment from physical trauma to the GI system with the repetitive retching [16]. HG patients often suffer from various degrees of dehydration, with a significant risk of hypovolemia and associated acidosis [16]. Severely ill patients can experience pre-renal renal impairment, severe vitamin deficiencies, including thiamin and vitamin K deficiencies, which have been linked to coagulopathies while thiamin deficiency has been cited to lead to Wernicke's Encephalopathy (WE) [16,21,23]. WE is an acute neuropsychiatric disorder that is derived from the severe thiamin deficiency that HG patients easily acquire due to the repeated and prolonged vomiting that they experience [17,20]. The condition of WE is typically not diagnosed until post-mortem at autopsy, the incidence of WE in relation to HG is relatively unknown and should be broadcast to all physicians that may encounter HG to help avoid this life-threatening but avoidable condition [20].

Infants resulting from HG pregnancies are associated with poor perinatal outcomes, including, preterm birth, low birth weight, fetal growth restriction and increased time in neonatal care units [21]. There is limited research in the influence HG can have on the fetus past the neonate period, however, there is evidence of HG playing a role in neurodevelopment delays [21,22]. While there is more research required to investigate the possible etiology of HG and how it may cause neurodevelopment issues, currently there is research that supports HG long-term consequences from these

pregnancies can produce an increased risk of autism spectrum disorder, altered brain structure, and behavioral developmental delays [22].

Pathophysiological Theories & Risk Factors

Currently, there is no universally accepted cause for HG; however, there are several theories that indicate commonalities in affected individuals which are theorized to contribute to the pathophysiological development of the disease [1,3,4,12,13]. Over half a century has passed with little to no advancement in understanding the underlying cause as to why only certain individuals experience the symptoms of HG during pregnancy until very recently [4,12]. Of the many theories that have developed over the 50+ years of attempting to understand HG, specific genetic factors, hormonal changes, and possible gastrointestinal changes are among the most widely accepted [3-5]. The purpose of this section is not to give an in-depth review of each possible theory, but to give a current summary of each to better inform providers for their own understanding and discussion with patients, the theories are listed in order of most widely supported and researched.

Genetic

Of all the underlying causes of HG, a genetic link may be the closest to a known cause of the disease, having two (2) potential genes identified that are involved in the presentation of HG [3,5,6]. The two genes identified are *GDF15* and *IGFBP7* on chr19p13.11 and chr4q12, respectively; both of which are primarily involved in placentation, appetite, and cachexia [5,6]. *GDF15*, specifically, is a cellular stress-response hormone that is upregulated in tissues responding to nutrient deficiencies, hyperthyroidism, prolonged fasting, and infections [26]. Although the direct causal link between these genes and HG have not been established, the association between *GDF15* has gained traction in the belief that the *GDF15/GFRAL/RET* pathway is related to this condition as it encodes for a TGF-β superfamily member that is expressed in the trophoblast cells of the placenta [5,6,26]. This evidence supports the idea that the *GDF15* gene is seen as the most likely cause as higher serum concentrations are associated with anti-emetic use, second trimester vomiting, and hospitalizations in women; weight loss, taste aversion, pica, aversion to drinking water, and emesis in non-pregnant animal models [26]. However, in assessing the p-values for the association between *GDF15* and placenta, nausea, and vomiting, two studies conducted by Fejzo, et al expressed virtually no chance of relation to one another [5,26]. *IGFBP7* has been found to play a role in neuronal coordination between metabolic status and feeding behavior, causing food aversion, even with early starvation; a symptom commonly observed in HG patients [5,6]. It should be noted that paternal genes are not currently thought to play a role in the occurrence of HG, whereas maternal intergenerational inheritance has been observed [3,4,13,14].

One study found that of 1,224 patients with HG in California, 28% reported a history of HG in their mother, 19% in a sister, and 9% with at least two relatives with HG [4,14]. As there is a low population of individuals suffering from HG, the study provides strong support to the hypothesis of HG being genetically linked and passed down through generations [4,14].

Hormonal

Human Chorionic Gonadotropin (hCG) is often cited as a potential cause of HG symptoms within the field. This becomes troublesome when understanding that there is no direct association that has been found, when in fact, there have been over 81 studies on biomarkers reviewed which all failed to concretely prove there was a causality between hCG and HG symptoms [25]. Although there is no clearly researched pathophysiology to support this claim, HG is reported more frequently in cases with elevated hCG [4]. For example, HG is more prevalent in a molar pregnancy or a multiple pregnancy [12]. This leads researchers to believe that those experiencing HG with a single-fetus pregnancy might be secreting elevated levels of hCG from their endometrial syncytiotrophoblast. While many studies reference hCG as a potential pathophysiologic cause of HG, there is not enough current research to confirm this theory.

Gastrointestinal

There are numerous pathophysiological theories of HG relating to changes in the gastrointestinal system. One theory cites the concept of estrogen and progesterone causing relaxation of the lower esophageal sphincter during pregnancy, hypothesizing that this may lead to increased incidence of gastroesophageal reflux disease (GERD) symptoms (i.e., nausea) [3,12]. Another theory hypothesizes that increased estrogen causes a shift in pH in the upper gastrointestinal tract, thus leading to an increased risk of prior *Helicobacter pylori* infections producing ulcers during pregnancy [12].

Many theories have been proposed relating to gastric motility and gastric emptying in its relation to sex steroids, however, there have been multiple studies, which have expressed contradictions to what is expected to be seen and have therefore only caused more confusion regarding the subject [12]. Fluid secretion theories in the upper gastrointestinal tract have also been noted; one of which hypothesizes that HG is a result of distention due to excessive secretion and accumulation of fluid in the gut lumen, tying into the belief that excessive hCG may play an important role in HG pathophysiology [12].

Other Possible Risk Factors

There are many potential risk factors that have been associated with a higher likelihood to experience HG symptoms during pregnancy; the following list is not exhaustive but contains many of the commonly discussed risk factors.

- Increased placental mass in the setting of multiple gestations [3]
- History of experiencing nausea and vomiting outside of pregnancy from consumption of estrogen-containing medications [3]
- History of motion sickness [3]
- History of migraines [3]
- Having a first-degree relative who have experienced HG during pregnancy [3-5,14]

- Young maternal age [13]
- Primiparous mothers [13]
- Persons of color [13]
- Female infant sex [13]
- Higher BMI [13]
- History of allergies and/or restrictive diets [7,13]
- Asian heritage [13]
- Higher psychological distress [13]
- H. pylori [4,13]
- Higher intake of daily saturated fats [5]
- Pregnancy onset of Addison's disease [7]
- History of diabetes [7]
- History of asthma [7]
- History of autoimmune diseases and/or immune disorders [7]

Treatment Options and Associated Burdens

Although there is no established standard for treatment of HG, some successful initial treatments often begin with non-pharmaceutical methods, including increasing prenatal dosage of folate and wearing acupressure wristbands to reduce nausea [3]. Studies suggest either a bland diet with simple carbohydrates and low acidic fruits or a diet high in protein and dairy products may help reduce HG symptoms [6]. Physicians should advance their treatment discussion from food trigger discussion and non-pharmaceutical interventions to a step-by-step treatment plan if the above treatments fail [3]. First line pharmacological therapy involves H1 antihistamines (administered in combination with vitamin B6) through several dosing recommendations and is considered to be one of the few safe and most effective pharmaceutical therapies available [3]. Second line therapies involve the use of antihistamines as well as dopamine antagonists or serotonin antagonists, all of which can be paired with regular saline boluses if the patient experiences dehydration [3].

Current pharmacological recommendations are shown in Table 1 and summarized in Figure 1, and exhibit the limited variety and large cost associated with the current available drugs. While at-home IV fluid administration may be considered controversial to some practitioners, patients that are admitted inpatient due to severe symptoms are recommended to become NPO with hydration therapy paired with appropriate electrolyte and vitamin supplementation, especially IV thiamin administration [23]. However, if IV home treatments were more widely accepted by both physicians and insurance, it may be possible to avoid the need for inpatient stays and diminish the psychological and social strain this disease takes on patients. As most patients with HG experience hypovolemia and may require IV boluses paired with pharmacological therapy, the cost and strain can increase as they progress in their pregnancy [8]. Additionally, as many insurance plans do not cover at-home IV administration, treatment options can cost several hundred dollars for weekly, or even daily, treatments [8].

Of the available therapies, antiemetics are heavily relied upon in the treatment of HG symptoms. Until recently, the frequently prescribed antiemetic, Ondansetron (Zofran), was used often. However, recent research and reviews implicate this drug as a possible teratogen, leading to hesitancy in the use of this drug [15]. While much research has been placed into this allegation and the latest conclusion in 2020 concluded that the use of the drug and its minimal linkage to possible defects are far outweighed by the benefit of preventing HG symptoms and reducing the risk of maternal and fetal nutritional deficiencies [15,24]. Due to the fear behind the possibility of birth defects, many mothers are hesitant to use Zofran because of the negative connotation that past lawsuits have cast on the drug, and as one of the few inexpensive treatments options, patients continue to struggle to find affordable ways to treat their symptoms [15].

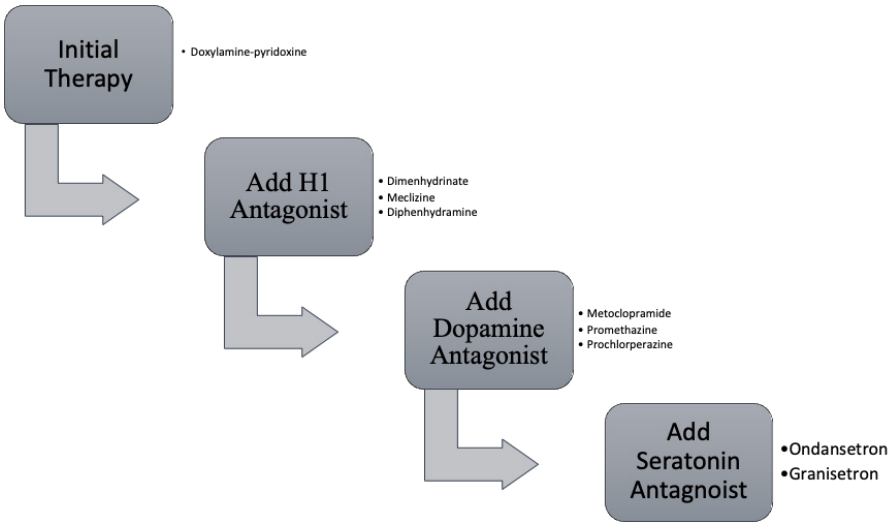

Figure 1: Suggested treatment action plan for patients with HG.

Table 1: Summary of treatment options for patients with HG.

Order of Intervention	Drug	Brand Name(s)	Pharmacological Category	Administration	Possible Adverse Effects	Pregnancy Considerations	Cost per Unit
Step 1 (Initial)	Doxylamine-pyridoxine	● Bonjesta ● Diclegis	First generation H1 antihistamine antagonist to treat nausea and vomiting in pregnancy	Oral with a strict dosing schedule	Palpitations, tachycardia, drowsiness, anorexia, constipation, diarrhea, dry mucous membranes, epigastric pain, xerostomia, dysuria, urinary retention, blurred vision, and/or diplopia.	Intended for pregnant patients and can be used without risk of fetal abnormalities.	$5.77 -$11.98
Step 2	Dimenhydrinate	● Dramamine ● Driminate ● GoodSense Motion Sickness	Ethanolamine derivative, first generation histamine H1 antagonist	Oral, IM, IV, or rectal	Tachycardia, dizziness, drowsiness, excitement, headache, insomnia, lassitude, nervousness, restlessness, skin rash, anorexia, epigastric distress, nausea, xerostomia, dysuria, blurred vision, and/or thickening of bronchial secretions.	Can cross the placental barrier.	**Solution:** $12.04/mL (50mg/mL dose) **Tablets**: $0.07
Step 2	Meclizine	● Antivert ● Bonine ● Dramamine Less Drowsy ● Motion-Time Travel Sickness ● Travel-Ease	Piperazine Derivative, first generation histamine H1 antagonist	Oral/Chewable	Drowsiness, fatigue, headache, vomiting, xerostomia, anaphylactoid reaction, and/or blurred vision.	Use has not resulted in an increased risk of fetal abnormalities.	$0.43- $4.31
Step 2	Diphenhydramine	● Over 15 brand names, most notable are: ● Benadryl Allergy Children's ● ZzzQuil	Ethanolamine derivative, first generation histamine H1 antagonist	Oral	Blurred vision, xerostomia, urinary retention, impotence, tachycardia, gastrointestinal effects, agitation, confusion, cognitive dysfunction, and/or delirium.	Can cross the placental barrier.	$0.02- $12.35
Step 3	Metoclopramide	● Gimoti ● Reglan	Antiemetic, Dopamine Antagonist	Oral, IV, or IM	Drowsiness, fatigue, lassitude, dizziness, and/or confusion.	Crosses the placental barrier and can be detected in cord blood and amniotic fluid.	$0.28- $214.29
Step 3	Promethazine	● Phenadoz ● Phenergan ● Promethegan	Antiemetic, First Generation Histamine H1 Antagonist, Phenothiazine Derivative	Oral, Rectal, IV, or IM	Blurred vision, confusion, constipation, dry eye, urinary retention, and/or xerostomia.	Crosses the placental barrier. Platelet aggregation may be inhibited in newborns.	$1.14- $35.77
Step 3	Prochlorperazine	● Compro	Antiemetic, First Generation Antipsychotic, Phenothiazine Derivative	Oral, Rectal, IV, or IM	Blurred vision, confusion, constipation, dry eye, urinary retention, and/or xerostomia. Jaundice, hyper/hyporeflexia have been reported in newborns following maternal use.	If used during the third trimester of gestation, there is a possibility of increased risk for abnormal muscle movements and withdrawal symptoms.	$0.59- $12.58
Step 4	Ondansetron	● Zofran ● Zuplenz	Antiemetic, Selective 5-HT3 Receptor Antagonist	Oral or IV	Constipation, headache, hypersensitivity reaction, and/or QT prolongation.	Crosses the placental barrier and can be detected in fetal tissue Risks related to suspected birth defects is currently under study.	$0.30- $106.51
Step 4	Granisetron	● Sancuso ● Sustol	Antiemetic, Selective 5-HT3 Receptor Antagonist	IV, SubQ, or Transdermal	Hypertension, QT prolongation, alopecia, skin rash, abdominal pain, constipation, anemia, dizziness, drowsiness, and/or fever.	Crosses the placental barrier. No adverse events have been observed in animal studies.	$7.50- $798.38

Conclusion

The gaps in the current healthcare system are evident in the treatment of patients who are affected by HG and are exhibited in the fear patients feel in seeking treatment from their healthcare providers due to the belief that their concerns and symptoms will be disregarded. This paper's aim is to highlight the patient experience and urge healthcare providers to bridge their gap in knowledge of HG to better support these vulnerable patients and to navigate this diagnosis. This paper highlighted the suspected etiology for providers to better understand and inform their patients as well as to recognize when an individual is suffering from HG. Additionally, this paper urges healthcare providers and researchers alike to strive to find better and affordable screening and solutions for their patients, as well as to know the available treatment options. Due to the severity of HG, it is imperative that healthcare providers stay up to date on the information needed to adequately treat their patients and support them in the condition termed by some patients as 'nine months of torture'.

References

1. Havnen GC, Truong MB, Do MH, et al. Women's perspectives on the management and consequences of hyperemesis gravidarum - a descriptive interview study. Scand J Prim Health Care. 2019; 37: 30-40.
2. Koudijs HM, Savitri AI, Browne JL, et al. Hyperemesis gravidarum and placental dysfunction disorders. BMC Pregnancy and Childbirth. 2016; 16: 374.
3. Jennings LK, Mahdy H. Hyperemesis Gravidarum. Stat Pearls. 2021.
4. London V, Grube S, Sherer DM, et al. Hyperemesis gravidarum: A review of recent literature. Pharmacology. 2017; 100: 161-171.
5. Fejzo MS, Sazonova OV, Sathirapongsasuti JF, et al. Placenta and appetite genes GDF15 and IGFBP7 are associated with hyperemesis gravidarum. Nat Commun. 2018; 9: 1178.
6. Lindberg R, Lindqvist M, Trupp M, et al. Polyunsaturated Fatty Acids and Their Metabolites in Hyperemesis Gravidarum. Nutrients. 2020; 12: 3384.
7. Mullin PM, Ching C, Schoenberg F, et al. Risk factors, treatments, and outcomes associated with prolonged hyperemesis gravidarum. J Matern Fetal Neonatal Med. 2012; 25: 632-636.
8. Mitchell-Jones N, Lawson K, Bobdiwala S, et al. Association between hyperemesis gravidarum and psychological symptoms, psychosocial outcomes and infant bonding: a two-point prospective case-control multicentre survey study in an inner city setting. BMJ Open. 2020; 10: 39715.
9. Shields KE, Lyerly AD. Exclusion of pregnant women from industry-sponsored clinical trials. Obstet Gynecol. 2013; 122: 1077-1081.
10. Christodoulou Smith J, Gold JI, Romero R, et al. Posttraumatic stress symptoms following pregnancy complicated by hyperemesis gravidarum. J Matern Fetal Neonatal Med. 2011; 24: 1307-1311.
11. Källén B. Hyperemesis during pregnancy and delivery outcome: A registry study. Eur J Obstet Gynecol Reprod Biol. 1987; 26: 291-302.
12. Verberg MFG, Gillott DJ, Al Fardan N, et al. Hyperemesis gravidarum, a literature review. Human Reproduction. 2005; 11: 527-539.
13. McCarthy FP, Lutomski JE, Greene RA. Hyperemesis gravidarum: Current perspectives. International Journal of Women's Health. 2014; 6: 719-725.
14. Fejzo MS, Ingles SA, Wilson M, et al. High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals. Eur J Obstet Gynecol Reprod Biol. 2008; 141: 13-17.
15. Kennedy D. Ondansetron and pregnancy: Understanding the data. Obstet Med. 2016; 9: 28-33.
16. Nana M, Tydeman F, Bevan G, et al. Hyperemesis gravidarum is associated with increased rates of termination of pregnancy and suicidal ideation: Results from a survey completed by >5000 participants. Am J Obstet Gynecol. 2021; 224: 629-631.
17. Fejzo M, Trovik J, Grooten IJ, et al. Nausea and vomiting of pregnancy and hyperemesis gravidarum. Nat Rev Dis Primers. 2019; 5: 62.
18. Jansen LAW, Koot MH, Dean CR, et al. The Windsor definition for hyperemesis gravidarum: A multistakeholder international consensus definition. Eur J Obstet Gynecol Reprod Biol. 2021; 266: 15-22.
19. Magtira A, Schoenberg FP, Mac Gibbon K, et al. Psychiatric factors do not affect recurrence risk of hyperemesis gravidarum. J Obstet Gynaecol Res. 2014; 41: 512-526.
20. Oudman E, Wijnia JW, Oey M, et al. Wernicke's encephalopathy in hyperemesis gravidarum: A systematic review. Eur J Obstet Gynecol Reprod Biol. 2019; 236: 84-93.
21. Martin C, Preedy V, Rajendram R. Development of corticospinal tract axons: from embryonic stage to adulthood. Elsevier Academic Press. 2021; 229-240.
22. Koren G, Ornoy A, Berkovitch M. Hyperemesis gravidarum – Is it a cause of abnormal fetal brain development? Reprod Toxicol. 2018; 79: 84-88.
23. Akinlaja O, Gist W. Nausea and vomiting of pregnancy and hyperemesis gravidarum. Obstetric Care. 2017; 308-314.
24. Huybrechts KF, Hernandez-Diaz S, Straub L, et al. Intravenous Ondansetron in pregnancy and risk of congenital malformations. JAMA. 2019; 323: 372-374.
25. Niemeijer MN, Grooten I, Vos N, et al. Diagnostic markers for hyperemesis gravidarum: A systematic review and metaanalysis. Am J Obstet Gynecol. 2014; 211: 1-15.
26. Marlena S Fejzo, Kimber W MacGibbon, Olivia First, et al. Whole-exome sequencing uncovers new variants in GDF15 associated with hyperemesis gravidarum. BJOG. 2022; 129: 1845-1852.