Hyperemesis Gravidarum: A Holistic Review and Approach to Etiopathogenesis, Clinical Diagnostic and Management Therapy

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REVIEW ARTICLE

Hyperemesis Gravidarum: A Holistic Review and Approach to Etiopathogenesis, Clinical Diagnostic and Management Therapy

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Abstract

Aim: To provide an overview of hyperemesis gravidarum (HG) and to present possible links between factors associated with the pathogenesis of HG also the effectiveness and safety of the nonpharmacologic and pharmacologic options available to treat HG.

Background: Although HG incidence is 0.3–2% worldwide, it is the number one cause of hospitalization in the first-trimester pregnancy, costs greatly to one financially, and also reduces the quality of life. This literature review focuses on articles published over the last 7 years to examine current perspectives and recent developments in HG.

Review results: Nausea and vomiting are common symptoms during early pregnancy. When vomiting is severe, it is referred to as HG. Despite its high prevalence, it tends to be underestimated. The etiopathogenesis remains unknown, but many risk factors have been determined. Currently, the therapy focused on improving the symptoms while minimizing risks to the mother and fetus. If HG is left untreated, it may lead to significant maternal morbidity and adverse birth outcomes.

Conclusion: Hyperemesis gravidarum is a complex and multifactorial condition. The incidence is higher in developing countries rather than in developed countries. Hyperemesis gravidarum can manifest as mild to severe signs and symptoms. The therapy ranges from dietary and lifestyle changes, intravenous fluid rehydration, hospitalization, nonpharmacologic, and pharmacologic treatment. Hyperemesis gravidarum can result as a mild to severe maternal and fetal complications.

Keywords: Etiopathogenesis, Hyperemesis gravidarum, Incidence, Outcomes, Treatment.

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Background

Hyperemesis gravidarum (HG) is excessive vomiting in pregnancy starting before the end of the 22nd week of gestation with or without metabolic disturbance such as carbohydrate depletion, dehydration, and electrolyte imbalance.[1] The most commonly cited criteria for the diagnosis of HG include persistent vomiting[2–8] (more than three times a day[9]) that is unassociated with other medical conditions,[4] dehydration[2–8] such as dry skin and lethargy,[7] ketonuria,[5–8,10] electrolyte imbalance (hypokalemia and hyponatremia),[2,4–8,10,11] and weight loss more than 5% of prepregnancy body weight.[4,6–8,10] Hyperemesis gravidarum incidence is 0.3–2% worldwide, but the number one cause of hospitalization in the first-trimester of pregnancy and costs greatly to one financially,[12] and also reduces the quality of life.[13]

Several risk factors associated with hyperemesis have been reported, such as nulliparity, juvenile pregnancy, multiple pregnancies, an anomaly of the fetus, female fetus, history of HG and other complications in a previous pregnancy, gastrointestinal tract infection, patient psychology factor, dysmenorrhea, and body weight.[2,3,13–15] Etiology and pathophysiology of HG are certainly unknown.[2,3,5,16,17] Several etiologies have been suspected play a role in HG, including elevated human chorionic gonadotropin (hCG),[3,4,7,8,11] estrogen, progesterone,[3,4,7] prostaglandin E2 (PGE2),[3,4] gastric dysmotility,[3,4] immunology, and inflammation[3,8] also infection of *Helicobacter pylori*.[3,4,7,8] Recent several studies show relations between HG and mild to severe maternal and fetal outcomes.[5,10,16,18,19]

First-line treatments of HG consist of simple lifestyle changes (eating small amounts often, avoid stimulating foods such as spicy foods, fatty foods, avoid stress, and get as much rest as possible),[20–24] doxylamine/pyridoxine combination,[20–23] ginger and acupressure at the pericardium P6 point.[20,23,24] Second-line treatments include a range of antiemetic drugs (metoclopramide, antihistamines, phenothiazines, and ondansetron)[20,23] also additional drugs such as antacids, H2 antagonists and proton-pump inhibitors (PPIs)[21] as well as the provision of intravenous fluid and electrolyte replacement for women who are dehydrated and ketotic.[22] Third-line treatments are reserved for patient with severe and persistent symptoms. These include corticosteroids and supportive therapy, such as enteral or parenteral feeding.[20,23,24] This journal review focuses on articles published over the last 7 years to examine current perspectives and recent developments in HG.

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Definition

Hyperemesis gravidarum is excessive vomiting in pregnancy starting before the end of the 22nd week of gestation with or without metabolic disturbance such as carbohydrate depletion, dehydration, and electrolyte imbalance.[1] Hyperemesis gravidarum is the most severe form of nausea and vomiting in pregnancy, and many cases require hospital admission and continuous treatment,[18] accompanied by more than 5% body weight loss, disturbance of electrolyte balance, ketonuria (80 mg/dL on urinary dipstick), and dehydration.[25–27] Excessive vomiting, use vomiting more than three times a day as their standard.[26,27]

Incidence and Risk Factors

Nausea and vomiting is a common symptom that happens in 50–90% pregnancies, and at least 1/3rd of the incidences need further treatment.[28] Meanwhile, HG incidence is only 0.3–2% worldwide. Hyperemesis gravidarum shows a variant incidence presentation in every country, wherein Swedish 0.3%, Norwegian 0.9%, Canada 0.8%, Malaysia 3.9%, and China 10.8%.[14] Some studies show a higher incidence in some ethnic groups.[7,14,28] In 8 million pregnancies, 61% are white, followed by Asian with 17% of the total.[26] Hyperemesis gravidarum population in East Asia itself is 3.9%.[14] In Indonesia, HG in pregnancy reachs 14.8%.[29] Even though it doesn't show a significant number of incidences, HG is the number one cause of hospitalization in the first-trimester pregnancy and costs greatly to one financially,[12] also reduces the quality of life.[13] Before 1940, HG caused maternal death in a significant number.[29] Based on the data taken in Indonesia; there is a significantly increased number of incidence of obstetric complications, included HG.[30]

From 8 million pregnant women, HG common occurrence obtained at 25–29 weeks gestation, followed by 20–24 weeks gestation.[31] Most HG patients had normal body mass index (BMI) (BMI 18.5–24.9), nonsmoking, with formal education >15 years. Mothers with low socioeconomic condition also have a higher incidence of HG.[14]

Several risk factors associated with hyperemesis have been reported, such as nulliparity, juvenile pregnancy, multiple pregnancies, an anomaly of the fetus, female fetus, history of HG and other complications in previous pregnancy, gastrointestinal tract infection, patient psychology factor, dysmenorrhea, and body weight.[2,3,13–15] Recent research suggests that gemili with both female fetuses may further aggravate the degree of HG.

There is a difference saying between journals was journal from Egypt writes that 94.6% of HG occurs in the first trimester (6–12 weeks), although in international journals it is said that HG in nulliparas mother happens more in their first trimester, whereas in multipar in the second trimester.[14,32]

Hyperemesis gravidarum tends to happen more in female fetuses. Female fetus has a higher level of ketonuria and a higher incidence of hospitalization. Some theory suggests that hCG levels at maternal levels are higher in the presence of female fetuses. There is no difference in serum urea level and hospitalization terms and reoccurrence in both.[7] For the male fetus, association with an increase in premature risk and neonatal morbidity is found.[33] It should be noted that the percentage of HG incidence in female and male fetuses didn't show a significant difference.[19,28,31,33]

There is an association between HG and a heavier weight of the placenta compared with birth weight. Female fetus gender also found as exacerbates factors.[19] Primary dysmenorrhea is defined as pain during menses in the absence of an identifiable pathologic lesion, which usually begins during adolescence. There is an association between adolescent and adult dysmenorrhea and HG.[15]

Psychological factors such as depression, anxiety, and stress are closely related to HG, but whether psychological factors are a risk factor or as a result of HG is still debatable. Some studies say that the effects of psychological abnormalities are only temporary and will disappear, 18 months after birth, some say the psychological disorder is settled and requires special attention to treatment.[34–36] However, psychiatric factors do not increase the risk of recurrent events for HG.[37]

H. pylori should be considered as one of the risk factors of HG, especially in developing countries. *H. pylori* is believed to have a contribution to the persistence of nausea and vomiting beyond the normal time course, dysmotility of the gastrointestinal tract and prolonged gastric emptying, and intestinal transit time. *H. pylori* infected the stomach of 50% of the world population, and it is more prevalent in developing countries.[38]

Results of a study implicated both underweight (BMI 5–20 kg/m^2) and obese prepregnancy BMI is a significantly increased risk of developing HG. Inadequate weight gain in the first trimester, as assessed by comparison of pre-pregnancy BMI and BMI during the first trimester, has been significantly associated with HG. In obesity, visceral adipose tissue (VAT) and prepregnancy BMI were correlated with the development of HG and hence could be considered as predictive markers for HG. Visceral adipose tissue is considered more specific than subcutaneous fat tissue (SCC).[39]

More than 28% of women with HG experienced recurrent events in the same pregnancy, and 26% experienced HG again in subsequent pregnancies. There was no association between HG and the long-term mortality of the fetus, as well as the risk of cardiovascular disease during adolescence.[33,40] In conclusion, HG is a complex, multifactorial condition with many potential etiological factors.[39]

Signs and Symptoms of Hyperemesis Gravidarum

Nausea and vomiting in pregnancy could be persistent and severe enough to require hospitalization to prevent maternal and fetal morbidity, this condition is known as HG.[2,3,7] Specific diagnostic criteria for HG are lacking,[7,8] but from several studies, the most commonly cited criteria for diagnosis of HG include persistent vomiting[2–8,10] (more than three times a day[9]) that unassociated with other medical conditions[4], dehydration[2–8] such as dry skin and lethargy,[7] ketonuria,[2–8,10] electrolyte imbalance (hypokalemia and hyponatremia),[2,4–8,10,11] weight loss more than 5% of pre pregnancy body weight[4,6,7,10] and severe signs and symptoms including orthostatic hypotension, tachycardia[7], hypovolemia,[10] muscle wasting,[2] mood changes and lethargy,[7] elevated from amylase, lipase, and functioning liver enzyme,[6,7] and an increase in hematocrit.[6] Severity of HG can be marked with the presence of severe ketonuria[7,34] (≥+3),[9,41] need for hospital admission,[2,3,41] early admission (<10 weeks of gestation), need total parenteral nutrition (TPN), and duration of hospitalization more than 2 days.[41]

Etiology and Pathophysiology of HG

Several studies have proposed to show that the etiology of HG is multifactorial.[2,4,7] Several factors have been suspected to play role of etiopathogenesis HG, including elevated of hCG,[3,4,7,8,11] estrogen,[3,4,7] progesterone,[3,4,7] PGE2, gastric dysmotility,[3,4] immunology, and inflammation[3,8,17] and infection of *H. pylori*.[3,4,7,8]

Human Chorionic Gonadotropin

Several studies have suggested that hCG indirectly causes HG by inducing thyroid hormones through thyroid-stimulating hormone (TSH) and estrogen (hormones are known to induce gestational emesis) by luteinizing hormone (LH).[3,4] One research from Dypvik et al. found mean maternal hCG serum concentrations in singleton pregnancies are 122 IU/L and 234 IU/L in twin pregnancies.[11] Another research from Garshabi et al. showed mean hCG serum concentrations in singleton pregnancies without HG and with HG is 150 IU/L and 210 IU/L.[42] In research from Atmaca et al., mean hCG serum concentrations in women with HG are 114 IU/L.[9] Research from Ghazali et al. showed mean hCG serum concentrations in women with HG are 173 IU/L.[43] According to that several research, HG typically present in a range of mean hCG serum concentrations between 114 IU/L and 210 IU/L in singleton pregnancies, while mean hCG serum concentrations in twin pregnancies is 234 IU/L.

Estrogen and Progesterone

Research from Al Ghazali et al. showed mean estradiol serum levels in patients with HG are 2,090 pg/mL.[43] Several proposed mechanisms of estrogen and progesterone are decreased gastric emptying, overall intestinal transit time,[3,7] gastric dysrhythmias, decreasing gastric smooth muscles contractility,[3,4,7] reducing intestinal motility, lower esophageal sphincter (LES) tone relaxation.[3,4]

Prostaglandin E2

Several studies have been shown a strong relationship exists between serum levels of PGE2 with HG.[3,4] PGE2 was found to affect HG by regulating gastric slow-wave frequency and peristaltic.[3]

Gastrointestinal Dysmotility

Pregnant women with HG have a more unstable electrogastrogram (EGG) activity than pregnant women without HG or nonpregnant women. Changes in EGG activity have been associated with clinical symptoms of HG.[4,6]

Immunology and Inflammation

During pregnancy, there is an increase in certain subsets of immune cells (granulocyte, natural killer cell, and T cells),[3,17] interleukin 4, interleukin 6 (IL-6), tumor necrosis factor α, immunoglobulin IgG and IgM, and complements have been found to be increased in HG.[3,17] Research from Desdicioglu et al. showed a significant increase of soluble urokinase-type plasminogen activator receptor (suPAR) and IL-6 in women with HG compared to women without HG as a control group.[17] According to that study results, increased levels of suPAR and IL-6 in HG group could be suggested associated with the etiopathogenesis of HG. That supported by some conditions such as steroid-using in HG patients shows dramatic improvement of the symptoms.[17,43]

H. pylori

Incidence of *H. pylori* infection in women with HG is about 90%.[4] In terms of the role of *H. pylori* on the pathogenesis of HG, it has been suggested that *H. pylori* may exacerbate hormone-induced changes in the nerve and electric functioning of the stomach. Local inflammation and produces toxins from colonizes bacterium are inducing severe vomiting in HG. Pathogenic strain from *H. pylori* is *cytotoxin-associated gene* A (CagA gene) that produces CagA protein, which induces mucosal damage and causes peptic ulcers. In this context, several studies reported that CagA positivity is more prevalent in patients with HG.[8]

Laboratory Findings and Diagnosis

The most commonly cited criteria for the diagnosis of HG include persistent vomiting not related to other causes, an objective measure of acute starvation (usually large ketonuria on urine analysis), electrolyte abnormalities, and acid-base disturbances such as hypochloremic alkalosis, hypokalemia, and hyponatremia, as well as weight loss.[7,20,22,44] Ultrasound examination may confirm viability and gestational age also identify a predisposing factor such as multiple pregnancies or molar gestation.[2,20,45]

Nausea and vomiting in HG can be categorized based on its severity using a validated questionnaire, known as pregnancy-unique quantification of emesis and nausea (PUQE) scoring index shown in Table 1.[7,20,22,46] Nausea and vomiting are categorized into three classes, mild, moderate, and severe. The total score is summed from the answers of each three questions. Categorized as mild, when the score is <6, moderate with a score of 7–12, and severe with a score of >13. Whereas from another literature, HG can be classified clinically into the level I, II, and III based on symptoms and physical examination.[8]

Management of Hyperemesis Gravidarum

Hospitalization is considered in patients with severe and persistent vomiting, weight loss, ketonuria, dehydration, and electrolyte disturbance.[22,47,48] Patients who are dehydrated and unable to take oral medications or fluids require intravenous fluid therapy.[20,45] The use of normal saline/NaCl 0.9% and ringer lactate (RL) is preferably[21,48,49] compared to dextrose because dextrose increases the incidence of Wernicke's encephalopathy.[21,44] Supplementation with thiamine 100 mg[7,21,48] may prevent the occurrence of Wernicke's encephalopathy.[7,20,45] Nutrition with enteral tube feeding (nasogastric, nasojejunal) was initiated in refractory cases, patients who were unresponsive to drug therapy and unable to maintain their weight.[22,44,46] Total parenteral nutrition was given to patients who did not respond to antiemetic therapy and can't be managed with enteral nutrition.[45,49]

Nonpharmacological Therapy of Hyperemesis Gravidarum

Mild cases of nausea and vomiting of pregnancy may be resolved with lifestyle and dietary changes. Common dietary recommendations include consumption of bland foods, eat small meals but often, avoid an empty stomach, avoid spicy and fatty foods,[2,20,22,46–50] give time between eating and drinking as well as drinking small and frequently.[46,48,49] Lifestyle modification involves

Table 1: Modified pregnancy unique quantification of emesis and nausea (PUQE)[20]

	1	*2*	*3*	*4*	*5*
Nauseated or stomachache	Not at all	<1 hour	2–3 hours	4–6 hours	>6 hours
Vomit	–	1–2 times	Times	5–6 times	>7 times
Dry heaves	–	1–2 times	3–4 times	times	>7 times

identifying and avoiding the triggers of nausea and vomiting,[20,44] preventing stress, and taking rest as much as possible.[20,46,49]

Psychotherapy and replacing iron-free multivitamins with folic acid supplementation may be recommended.[20,22,47–50] ACOG recommends ginger as a nonpharmacological intervention[20,44] that can improve nausea but not to reduce vomiting.[20–22,49] Ginger contains gingerol and shogaol that inhibit 5-HT3 serotonergic receptors and inhibit the growth of *H. pylori*.[45,50] Ginger available in powder, capsule, tablet, and syrup[37] with recommended doses of 250 mg 4 times daily peroral.[45,50] Ginger is found to be safe without an increase in major malformation.[20,46–50] Acupressure therapy in relieving nausea and vomiting, which performed on the pericardium 6 (P6/neiguan),[24,50] remains controversial.[45]

Pharmacological Therapy of HG

The effectiveness and safety of many optional medicines, shown in Table 2, are taken into consideration in the selection of pharmacological therapy for HG cases.

In the past, thalidomide was prescribed for the treatment of HG worldwide, especially in Europe, but the United States FDA rejected thalidomide in 1962 when the drug was released in 1957 because of its teratogenic effect that could cause congenital abnormalities of phocomelia.[8] ACOG recommends a combination of vitamin B6 (pyridoxine) and H1 antagonists (doxylamine) as a safe and effective first-line pharmacotherapy (category A).[20,45–47,49] Metoclopramide and promethazine have similar effectiveness in reducing nausea and vomiting, but the side effects are lower in the use of metoclopramide.[20,21,45,48] Antihistamines or H1 receptor antagonists such as dimenhydrinate and diphenhydramine (category B) that work indirectly to the vestibular system by reducing stimulation in the vomiting center are also frequently used and proven to be effective without risk to the fetus.[20,22,50] The use of metoclopramide, promethazine, or antihistamines during pregnancy does not increase the risk of congenital malformation.[20–22,45,47]

5-hydroxytryptamine3 (5HT3) receptor antagonists such as ondansetron are beginning to be used frequently. Ondansetron has the same effectiveness as promethazine and metoclopramide, but its side effects are smaller.[20,45] Several studies have reported the occurrence of cleft palate and heart defects, on the use of ondansetron[48,50] methylprednisolone may be an option for refractory cases.[20,21,45,50] In one study, it was found that the use of methylprednisolone in the first trimester was associated with cleft palate risk.[7,20,22,45–47,49,50] Steroid use should be avoided before 10 weeks of gestation.[20,45,49,50] H2 receptor antagonists such as ranitidine (category B), and PPI such as omeprazole (category C), are often used for reflux management when antacids failed to overcome. Its use is unrelated to an increased risk of major malformations.[21,47,50]

Table 2: Fetal safety of pharmacologic agents used to treat nausea and vomiting of pregnancy[44]

Pharmacologic class/ agent	*Risk classification*	
	FDA risk factor	*Briggs et al.*
Doxylamine succinate/pyridoxine hydrochloride	A	Compatible
H1-receptor blocker		
Dimenhydrinate	Not rated	Compatible
Diphenhydramine	Not rated	Compatible
Doxylamine	Not rated	Compatible
Meclizine	Not rated	Compatible
Hydroxyzine	Not rated	Human data suggest low risk
Meclizine	Not rated	Compatible
Metoclopramide	B	
Phenothiazine		
Prochlorperazine	Not rated	Compatible
Promethazine	C	Compatible
Ondansetron	B	Human data suggest low risk
Pyridoxine hydrochloride	A	Compatible
Corticosteroid	C	Human data suggest risk; avoid during first 10 weeks of gestation

Note: A: adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimester); B: animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester; C: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of drug in pregnant women despite potential risks

Therapeutic Treatment of Nausea and Vomiting of Pregnancy

Therapeutic treatment assumes other causes of nausea and vomiting have been ruled out. At any step, consider enteral nutrition if dehydration or persistent weight loss is noted.

- Some antiemetic medications have only been approved by the US Food and Drug Administration for use in nonpregnant patients; however, off-label use is common. Obstetricians and other obstetric care providers should counsel patients and document such discussions accordingly. Care should be exercised if multiple antiemetic medications are used simultaneously. Parallel use of some medications (see text) may result in an increased risk of adverse effects.
- In the United States, doxylamine is available as the active ingredient in some over-the-counter sleep aids; one half of a scored 25 mg tablet can be used to provide a 12.5 mg dose of doxylamine.
- Thiamine, intravenously, 100 mg with the initial rehydration fluid and 100 mg daily for the next 2–3 days (followed by intravenous multivitamins), is recommended for women who require intravenous hydration and have vomited for more than 3 weeks to prevent a rare but serious maternal complication, Wernicke encephalopathy.[20]

Hyperemesis Complications

Maternal Complications

Several maternal complications from HG such as severe malnutrition,[2,3,7] anemia,[18] Wernicke's encephalopathy,[4,7,10] peripheral neuropathy,[2–4] coagulopathy,[2,4,7] venous thromboembolism (VTE).[9] And some rare complications such as acute kidney injury[10] that marked as oliguria, esophageal rupture,[3,4,7] Mallory–Weiss

syndrome, pneumomediastinum,[3,7] rhabdomyolysis,[4,7,10] and demyelination syndrome such as central pontine myelinolysis.[4,7]

This deficiency of thiamine or vitamin B1 may lead to a syndrome called Wernicke's encephalopathy.[4,7] Patients may present with neurological symptoms from lethargy and confusion[4,7] to hyporeflexia,[7] ataxia, and oculomotor symptoms including nystagmus and ophthalmoplegia,[4,7] and convulsion.[4] If Wernicke's encephalopathy is suspected for a patient, MRI may be useful in the diagnosis and identifying other severe complications such as central pontine myelinolysis.[7] Central pontine myelinolysis is a demyelinating of the central pons while preserving the axons. This condition present due to prolong hyponatremia and rapid correction of natrium.[4] A case report patient with HG who got a central pontine myelinolysis that published by Anand et al. has shown upper limits have been set for correction of hyponatremia: 8 mEq/L in 24 hours, 14 mEq/L in 48 hours, and 16 mEq/L in 72 hours. The pathophysiology of myelinolysis is attributed to hyperosmotic stress produced by rapid correction of hyponatremia, which causes endothelial injury and damages the blood–brain barrier resulting in release of myelinotoxic factors.

Coagulopathy is present from vitamin K deficiency.[4,7] Peripheral neuropathy is also present due to vitamin B6 and B12 deficiency.[4] VTE and acute kidney injury that is present in HG can be caused due to prolonged dehydration.[18] Several studies have shown rhabdomyolysis caused by hypokalemia.[4,7,9] In severe cases, rhabdomyolysis can cause acute kidney injury by leakage of muscle-cell contents (myoglobulin) in the urine.[4,9] Other rare complications of HG are esophageal rupture that marked as hematemesis (known as Mallory–Weiss syndrome) that caused due to repetitive wrenching of gastrointestinal mucosal and barotrauma (Boerhaave syndrome).[7] Esophageal rupture may lead to complications such as pneumomediastinum (free air in the mediastinum) (Hamman's syndrome).[4,7] Several studies have been shown relations between HG and depression, anxiety and post-traumatic syndrome.[9]

Fetal Complications

Hyperemesis gravidarum has been reported to be associated with low birth weight (LBW),[3,7,16,18,19] preterm birth (PTB),[3–8,16,18,19] small-for-gestational-age (SGA),[3,5,8,10,16,18,19] intrauterine growth restriction (IUGR),[5,16] preeclampsia,[3,5,7,10,18] and placental abruption.[3,5,7,18] A recent meta-analysis on HG and pregnancy outcomes, comprising 13 case-control studies, 10 cohort studies, and one cross-sectional study, reported that HG was associated with a 30% increase in risk for PTB and SGA, and 40% increase in risk for LBW.[16] Women with HG gaining less than 7 kg during pregnancy had a threefold increase in risk for PTB and LBW.[3,4,7,16] American case-control study found women with HG, to gain on average 4.6 kg less during pregnancy and to deliver babies, who weighed on average 172 g[5,7] to 291 g[16] less compared to those born from healthy women.[16] Other studies showed women with HG more common preterm delivery in gestational age <37 weeks[7,41] with the babies deliver in LBW.[16]

Several studies have been shown that exposure HG *in utero* associated with risk for the psychological and behavioral disorder[4,7,10] (attention-deficit disorder, depression, bipolar disorder, and anxiety) and neurodevelopmental disorder[4] (speech or language delay, social development delay, autism, and central auditory disorder) in children. Overall, 49% of women with HG reported at least one child with an emotional, behavioral, or learning disorder. The United Kingdom Childhood Cancer Study (UKCCS) found a 3.6-fold increase in risk for all forms of leukemia (acute lymphatic leukemia and acute myeloid leukemia) in children who exposed with HG compared to children who unexposed to HG *in utero*. An America study reported that hyperemesis was associated with a four-fold increase in testicular cancer risk among male offspring. A possible mechanism is hCG, which increases in HG can act as a growth factor, and estrogen may also be oncogenic to hematopoietic cells.[19]

According to several data, the most common fetal complications include PTB <37 weeks, LBW, and SGA. And the most common fetal long-term complications are depression, anxiety, and bipolar disorder in children who exposed to HG *in utero*.

Discussion

There is no exact definition of HG, as it is hard to meet the agreement of excessive vomiting term. Many journals agree that excessive vomiting is the one that causes a metabolic disturbance such as dehydration and electrolyte imbalance, but the WHO states that excessive vomiting could happen with or without metabolic disturbance. To measure excessive vomiting, most journals use vomiting >3 times as their standard. Incidence in each country seems to contradict incidence rate based on ethnic, wherein Asian countries show a higher incidence rate, but based on ethnicity, Asian percentage is lower than white people. This happens because the research of ethnic rate was done in a country, where white is the dominant population further, research needs to be done. As for risk factor that affects the most in HG, still, need further research.

Hyperemesis gravidarum is present in the first trimester of pregnancy[2–4] (starts within 4 weeks after the last menstrual period,[3,5] and typically peaks around 9 weeks of gestation[3,5,6] and usually resolves by 12 weeks and 20 weeks of gestation[3,4,41]). Clinical research and medical practice have yet to adopt a universal system of HG classification, the clinical diagnosis.[7,8] However, HG is clinically classified as mild and severe, whereas a severe symptom is depending on associated metabolic disturbances such as carbohydrate depletion, dehydration, and electrolyte imbalance.[2] From several signs and symptoms that entered into HG criteria, signs and symptoms of dehydration with or without orthostatic hypotension consistently found in a physical examination in patients with HG.

Progress in the understanding of the etiology and pathophysiology of HG has been slow in recent decades. Until now, there is no major etiopathogenesis, which having strong evidence to cause HG, so that is the multifactorial etiology still believed as a cause of HG.[4,8,41] A meta-analysis of published studies investigating the correlation between increased serum levels of hCG and HG between 1966 and 2005, noted that out of 18 published studies, 11 showed a positive association. However, direct role of mechanism of hCG causes HG is still unclear. Estrogen and progesterone, which increase dramatically in pregnancy, have also been implicated in the etiopathogenesis of HG. Several studies have shown that some women experience nausea when taking oral contraceptives, which typically contain a combination of estrogen and progesterone. That conditions also support the hypothesis of estrogen and progesterone as an etiology of HG.[7]

Gastrointestinal dysmotility is a condition that causes symptoms of HG, which have an association with hormone estrogen and progesterone.[3,4,7] The role of immunological homeostasis has also been explored. Functional activation of these cells has been speculated to play a role in pregnancy-associated disorders, including hyperemesis.[3,17] Pregnancy causes immunological changes, including diminished cell-mediated immunity, hence

making her more prone to infections, such as *H. pylori*.[8] *H. pylori* infection of the stomach has also been associated with an increased incidence of HG.[3,7,8] A recent study in the Netherlands demonstrated that women who were *H. pylori* positive were more likely to report daily vomiting with an adjusted odds ratio of 1.44.[7] Another meta-analysis study has shown a significant association between *H. pylori* infection with HG (odds ratio 3.32).[10]

Hyperemesis gravidarum is diagnosed by excluding other causes of the symptoms.[7,20,21] It is critical to have a graded scale to track the severity of symptoms as a guide to determine the appropriate treatment and response to treatment. Currently, there is no consensus on the definition of HG, and there is no single, widely used set of diagnostic criteria for diagnosing HG.[44] Advice for women experiencing NVP has traditionally revolved around dietary changes. However, there is limited evidence supporting the effectiveness of dietary changes on relieving NVP symptoms. Many authors review different classes of antiemetic used to treat this condition and discuss that some have better safety profiles than others, but most appear to be safe to use in pregnancy. Firstly nonpharmacological treatment should be advised. Antiemetic and steroid treatment should be considered latter.[2] Studies on therapeutics for refractory HG are few in number, suggesting opportunities for further research in this arena.[7]

Hyperemesis gravidarum can cause maternal complications due to electrolyte disturbances, prolonged dehydration, malnutrition, and end-organ damage.[8,10] Several studies have been shown relations between HG and depression, anxiety, and posttraumatic syndrome.[8,10] Psychological and behavioral disorders in women with HG associated with regulation changes of neuroendocrine and neurotransmitters in the brain and abnormal programming of the hypothalamic-pituitary-adrenal axis (HPA-axis). A recent meta-analysis of 37 cohort studies and 18 case-control, including 3.5 million women and other studies reported that low total gestational weight gain was associated with increased risks for PTB, LBW, SGA, and IUGR.[4,7,16] A research from Peled et al. reported that female fetuses more commonly have IUGR, while male fetuses associated with increased risk for prematurity and neonatal morbidity.[41] Poor maternal health due to HG and fetal exposure to hormones induced by HG suggested to play a role of fetal complications in women with HG.[4] Also, the most common fetal long-term complications are depression, anxiety, and bipolar disorder in children who exposed to HG *in utero*.

Conclusion

Hyperemesis gravidarum is a complex, multifactorial condition with many potential etiological factors. The incidence is higher in developing countries rather than in developed countries. HG can manifest as a mild to severe signs and symptoms due to prolonged dehydration and decrease of nutritional intake that make the patients with HG need for hospitalizations. It is the number one cause of hospitalization in the first-trimester pregnancy. The understanding of the etiopathogenesis of HG remains unclear. But, several studies and research have shown correlations between a number of factors that suggested to play in the role in a etiopathogenesis of HG with the presence of HG. A focus on the assessment is to confirm that nausea and vomiting are due to the pregnancy and not some other causes. Adoption of an easy, objective and validated tool can be helpful to assess severity and treatment impact such as PUQE. The therapy ranges from dietary and lifestyle changes, intravenous fluid rehydration, hospitalization, nonpharmacologic, and pharmacologic treatment. HG can result in mild to severe maternal and fetal complications.

Clinical Significance

There were significant results in reducing nausea and vomiting with acupressure therapy.[21,22,49,50] Some studies have reported that ginger is more effective than a placebo and is as effective as pyridoxine,[49,50] while other studies have found that ginger is more effective than pyridoxine,[21] but no substantial evidence to suggest that the combination of pyridoxine and doxylamine is more effective than other antiemetic. Metoclopramide is effective, economical, has a long history of widespread use, has an excellent fetal safety record, and remains a reasonable first-line short-term antiemetic choice in HG despite ondansetron. Patients with steroid therapy are less likely to be readmitted.[5,20,44,46,47,49]

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