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The evidence bases of etiopathophysiology and preventive clinical management of nausea and vomiting in pregnancy

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Nausea and vomiting, or early gestosis, is a common disorder during pregnancy, affecting up to 80% of pregnant women. The severe form is known as excessive vomiting of pregnancy – hyperemesis gravidarum (HG) and is a debilitating and potentially life-threatening illness during pregnancy which is characterized by persistent nausea and/or vomiting, weight loss, malnutrition and dehydration, increases the risk of adverse maternal and perinatal outcomes. Without the methodical intervention of experienced clinicians, life-threatening complications can develop. Effective prevention and treatment strategies for HG require an understanding of both pathophysiological and psychosocial factors, awareness of potential risks and complications, and proactive assessment and treatment methods using innovative clinical tools. HG is characterized by dehydration, electrolyte and metabolic imbalance, as well as nutritional deficiency, which can lead to hospitalization. The severity of nausea and vomiting during pregnancy can be assessed using the Unique Gestational Vomiting Qualification (scale PUQE-24), which has been shown to be a relatively accurate assessment of the patient's lifestyle, including hours of sleep.

For high-quality differential diagnosis, a focused anamnesis collection and examination are necessary, since the diagnosis of this condition is mainly determined clinically. Laboratory tests are useful tools for evaluating complications such as electrolyte or metabolic imbalances or kidney damage. In addition, they help to determine the etiology in refractory cases.

Hypotheses that contribute to the understanding of the pathogenesis of HG have been based on associations that are causal, sequential, or coincidental. Much efforts are needed to precisely establish these relationships in well-designed studies. HG is the most common indication for hospitalization in the first half of pregnancy. Numerous nutrient deficiencies have been identified, such as thiamine deficiency, which can lead to Wernicke's encephalopathy, vitamin K deficiency, and severe hypokalemia.

It is noteworthy that, in addition to the above-mentioned physical complications, HG is also associated with psychological adverse consequences. Although it has been associated with serious complications, HG prognostic factors are not studied well.

The purpose of this systematic review was to find and critically evaluate studies that determined the priority areas of clinical management of vomiting in pregnant women, based on the differentiation and pathophysiological component, the analysis of the safety profile of non-pharmacological agents to prevent the development of the above-mentioned gestational pathology, and the clarification of an effective strategy of interprofessional teams to improve care coordination and outcomes in pregnant women with nausea and vomiting.

A systematic data search was carried out in the databases MEDLINE, ISI Web of Science, PubMed, Scopus, Google Scholar, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects and publications in professional editions of Ukraine for 2010–2023.

The main result was the prediction of the occurrence of vomiting in pregnant women and HG, the effectiveness of preventive intervention, the reduction or cessation of nausea/vomiting; the number of episodes of vomiting; duration of hospitalization. Secondary outcomes included other parameters of preventive strategy effectiveness, adverse maternal/fetal/neonatal outcomes, quality of life measures, and economic costs. Preventive measures: ginger, acupressure/acupuncture, diet, hypnotherapy. The economic evaluation of prevention strategies also took into account perinatal outcomes. Therapeutic strategies, primarily infusion therapy, will be reviewed and analyzed by us in the following review.

The results of evidence-based medicine presented in the reviews can be used in the creation of a clinical guideline, protocol, consensus or clinical recommendations regarding the clinical management of nausea, vomiting of pregnancy and HG.

Keywords: *pregnancy, vomiting of pregnancy, hyperemesis gravidarum, ketonuria, ketosis, scale PUQE-24, dehydration, acupuncture, Wernicke's encephalopathy, ginger, hypnotherapy, perinatal pathology, endodermal cancer, hypothyroidism, trophoblastic disease.*

Доказові основи етіопатофізіології та превентивного клінічного менеджменту нудоти та блювання вагітних

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Нудота та блювання, або ранній токсикоз, є поширеним розладом під час гестації, на який страждають до 80% вагітних. Тяжка форма відома як надмірне блювання вагітних (НБВ) і є виснажливим та потенційно небезпечним для життя захворюванням під час вагітності, що пояснюється невпинною нудотою та/або блюванням; характеризується втратою маси тіла, недоїданням та зневодненням, підвищує ризик несприятливих наслідків для матері та дитини.

Без методичного втручання досвідчених клініцистів можуть розвинутися небезпечні для життя ускладнення. Ефективні профілактичні та лікувальні стратегії НБВ вимагають розуміння як патофізіологічних, так і психосоціальних факторів, усвідомлення потенційних ризиків та ускладнень, а також проактивного оцінювання та методів лікування з використанням інноваційних клінічних інструментів. НБВ характеризується зневодненням, електролітним і метаболічним дисбалансом, а також дефіцитом харчування, що може стати приводом до госпіталізації. Тяжкість нудоти та блювання під час вагітності можна оцінити за допомогою унікальної кваліфікації блювання під час гестації (шкала PUQE-24), яка продемонструвала відносно точну оцінку способу життя пацієнтки, включаючи години сну.

Для якісної диференціальної діагностики необхідні цілеспрямований збір анамнезу та обстеження, оскільки діагноз цього стану переважно визначається клінічно. Лабораторні дослідження є корисними інструментами для оцінювання таких ускладнень, як електролітний або метаболічний дисбаланс чи ураження нирок. Крім того, вони допомагають визначити етіологію у рефрактерних випадках.

Гіпотези, які сприяють розумінню патогенезу НБВ, ґрунтувались на підставі асоціацій, які є причинно-наслідковими, послідовними або випадковими. Необхідно докласти багато зусиль, щоб точно встановити ці взаємозв'язки у рамках добре спланованих досліджень. НБВ є найпоширенішим показанням до госпіталізації у першій половині вагітності. Виявлено численний дефіцит поживних речовин, таких, як дефіцит тіаміну, який може призвести до енцефалопатії Верніке, дефіцит вітаміну К і тяжка гіпокаліємія.

Примітно, що окрім зазначених вище фізичних ускладнень, НБВ також асоціюється з психологічними несприятливими наслідками. Хоча це було пов'язано з серйозними ускладненнями, мало відомо про його прогностичні фактори.

Метою даного систематичного огляду був пошук та критичне оцінювання досліджень, які визначали пріоритетні напрямки клінічного менеджменту блювання вагітних, виходячи з диференціації та патофізіологічної складової, аналіз профілю безпеки нефармакологічних засобів, що були використані для профілактики розвитку наведеної вище гестаційної патології та роз'яснення ефективної стратегії міжпрофесійної команди для покращення координації догляду та результатів у вагітних із нудотою та блюванням.

Проведений систематичний пошук даних по базах MEDLINE, ISI Web of Science, PubMed, Scopus, Google Scholar, Cochrane Database of Systematic Reviews й Database of Abstracts of Reviews of Effects та публікацій у фахових виданнях України за 2010–2023 рр.

Основним результатом було прогнозування виникнення блювання вагітних та НБВ, ефективності превентивного втручання, зменшення або припинення нудоти/блювання; кількості епізодів блювання; тривалості госпіталізації. Вторинні результати включали інші показники ефективності превентивної стратегії, несприятливі результати для матері/плода/неонатального періоду, показники якості життя та економічні витрати. Профілактичні заходи: імбир, точковий масаж/голковколювання, дієта, гіпнотерапія. Економічна оцінка стратегій профілактики ураховувала й перинатальні результати. Терапевтичні стратегії, насамперед інфузійна терапія, будуть нами розглянуті та проаналізовані у наступному огляді.

Представлені в оглядах результати доказової медицини можуть бути використані при створенні клінічної настанови, протоколу, консенсусу або клінічних рекомендацій стосовно клінічного менеджменту нудоти, блювання вагітних та НБВ.

Ключові слова: *вагітність, блювання вагітних, надмірне блювання вагітних, кетонурія, кетоз, шкала PUQE-24, зневоднення, акупунктура, енцефалопатія Верніке, імбир, гіпнотерапія, перинатальна патологія, ентодермальний рак, гіпотиреоз, трофобластична хвороба.*

Pregnancy nausea and vomiting, or early gestosis (EG), is diagnosed in 80.0% of pregnant women. EG is characterised by symptoms of varying severity, usually occurring in the 5-6th week of pregnancy, and mostly resolving by the end of the first trimester [1-3]. As many as 90.0% of pregnant women experience nausea.

Other studies report that approximately 27.0 to 30.0% of women experience only nausea, while 28 to 52.0% of all pregnant women experience vomiting. For the majority of these women, however, preventive treatment is sufficient to avoid the progression of normal EG to severe pathology and hyperemesis gravidarum (HG), which affects 0.6 to 3.2% of women [35].

Currently, there is no universally accepted point at which nausea and vomiting in pregnancy progresses to HG. The last one is associated with a variety of metabolic disorders, such as carbohydrate depletion, dehydration, or electrolyte imbalance [78]. Moreover, the severe symptoms of HG cause a serio us psychosocial burden, leading to depression, anxiety, and even to pregnancy interruption. EG and HG are the most common indications for hospitalisation in the first half of pregnancy and are second only to preterm delivery as a cause of hospitalisation during pregnancy.

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Clinically, HG is a diagnosis of exclusion, which is characterised by prolonged and severe nausea and vomiting, dehydration, ketonuria and/or ketonaemia, and a loss of more than 5% of body weight. There are no commonly accepted diagnostic criteria for this condition, but they are usually determined by the severity/duration of nausea and vomiting. The role of the interdisciplinary team in the prevention and treatment of HG of should be emphasised.

Though EG and HG are frequent problems in pregnant women, there are few studies focusing on the pathogenesis. The reason may be that EG is often considered as a normal and self-limiting condition, but the burden of EG and HG is largely underestimated. More recent studies have shown that most clinical trials and other researches related to HG raise awareness and support for pregnant women, which is critically important for further efforts to solve this problem [45].

HG has been shown to negatively impact health and well-being of women who suffer from weight loss, nutritional deficiencies, acidosis and ketonuria, fatigue, frustration, resentment and depression. These women report a significant deterioration in their quality of life: inability to take care of themselves, their children and family, to work and socialise. Sometimes, these symptoms lead women to consider abortion or to avoid another pregnancy after HG [40].

In 1956, a panel appointed by the American Pharmaceutical and Chemical Boards first defined HG as refractory vomiting and a group of disorders including electrolyte balance changes, weight loss ≥5%, ketosis and ketonuria, neurological disorders, liver damage, retinal haemorrhage, and kidney damage.

A recent international consensus definition for HG (2019) consists of: symptoms start in early pregnancy (before 16 weeks gestational age); nausea and vomiting, at least one of which is severe; inability to eat and/or drink normally; strongly limits daily living activities. Signs of dehydration (weight loss, electrolyte deficiency) are considered to be crucial for HG [21].

J. N. Robinson et al. (1998) reported that malnutrition in pregnant women due to HG can lead to vitamin K deficiency, which in turn can cause blood clotting disorders [67]. In addition, HG is potentially associated with many serious complications, including Wernicke's encephalopathy (a consequence of vitamin B_1 deficiency), acute liver and kidney failure, oesophageal rupture, pneumothorax, and later preeclampsia, placental abruption, and fetal growth retardation. Other adverse effects include premature birth, small for gestational age fetus, electrolyte disturbances that can lead to cardiac arrhythmia, neuromuscular and renal complications, thyrotoxicosis, and even death [9, 21, 45].

The studies in this review found evidence that some prevention methods (ginger, acupressure, diet, acupuncture, hypnosis) were better than placebo for moderate symptoms of nausea and vomiting during pregnancy, but there is little evidence or conflicting opinions on the efficacy of treatments for EG and HG [3, 35, 47, 49, 74].

Therefore, the literature review presented here aims to:

- identify priority areas for the clinical management of pregnancy vomiting based on differentiation and pathophysiological component,
- assess the safety profile of non-pharmacological treatments used to prevent this gestational pathology and its complications,
- provide effective strategies for the multidisciplinary team for improvement of the quality of care for pregnant women with nausea and vomiting and, ultimately, maternal and perinatal outcomes.

Data sources. Randomised, controlled trials were identified by searching in the electronic databases MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, Allied and Complementary Medicine Database, Science Citation Index, Social Sciences Citation Index, Scopus, Conference Proceedings Index, NHS Economic Evaluation Database, Health Economic Evaluation Database, China National Knowledge Infrastructure, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects, and publications in Ukrainian professional journals. The search was conducted from the beginning of 2010 to February 2023. Obstetric sections were checked manually, as well as the websites of relevant organisations.

Review methodology. The key criterion that was taking into account in the sources was the efficacy of the preventive intervention, defined by the dynamics of the severity of the general state, reduction in the number of episodes or duration of nausea/vomiting; cessation of vomiting; number of days of hospitalisation. Secondary outcomes included intervention efficacy measures such as adverse maternal/fetal/neonatal outcomes, quality of life, and economic costs. Preventive measures included: ginger, acupressure/acupuncture, diet, hypnotherapy. The economic evaluation of prevention strategies accounted for perinatal outcomes.

The consensus of all authors was used to make the final decision when making recommendations. Any conflict that arose was resolved after discussion with all authors.

Aetiology and pathophysiology of HG

There are risk factors for EG and HG during pregnancy. Some researchers reported that the incidence of HG was 40% higher in women under 20 years old, primipara patients, women with <12 years of education, non-smok-

ers, and obese women. Some confounding factors, such as family income, parity, and oral contraceptive use prior to pregnancy, may also be associated with the severity of HG [45]. It has been reported that the incidence of HG in the I trimester of multiple pregnancies is higher compared to singleton pregnancies [19].

An increase in placental weight in molar or multiple pregnancies is associated with a higher risk of HG. In addition, women with a history of nausea and vomiting outside of pregnancy due to the use of oestrogen-containing products, coordination disorders or migraines have a higher risk of nausea and vomiting during pregnancy. Some studies also suggest a higher risk of HG in women who have a first-degree relative, such as a mother or sister, who has suffered from pregnancy hyperemesis.

Human chorionic gonadotropin (hCG) is a pregnancy hormone secreted by the placental cytotrophoblast cell layer and is associated with fetal growth and various placental, uterine and fetal functions [30]. hCG is considered to be an essential factor in the pathogenesis of HG. This opinion is mainly based by the coincidence of peaks in hCG production and symptoms of HG at the 12th and 14th weeks of gestation [11].

Prospective studies have reported that serum hCG level was significantly higher in patients with HG than in other EG forms. It is believed that hCG can provoke the development of HG by stimulating hypersecretion in the upper digestive tract. However, one should be careful of a causal relationship, because the role of hCG in the pathogenesis of HG is not yet clear, and furthermore, other conditions with high hCG level, such as choriocarcinoma, do not manifest as vomiting, and some pregnant women with high serum hCG concentration do not complain of vomiting [23].

The researchers have found that some patients have a mutation in the extracellular domain of the receptor, making them sensitive even to normal serum hCG level [68]. Additionally, high hCG have been found to be associated with fetal growth retardation and preterm birth, while EG and HG are likely to have a protective effect for preterm birth. This makes it unlikely that hCG is the only factor contributing to the pathogenesis of HG [82]. Specific genetic studies have not found evidence of a link between HG and hCG or its receptor [64].

Estradiol level is increased in early gestation and decreased later, mirroring the typical course of nausea and vomiting during pregnancy. One study found a positive association between nausea and vomiting and maternal serum estrogen level [74]. Increased serum concentration of steroid hormone is assumed to cause a decrease in intestinal motility and gastric emptying, which in turn changes the pH of the digestive tract and stimulates the development of subclinical *Helicobacter pylori (H. pylori)* infection.

However, a review of 17 studies found that only five of them demonstrated a positive correlation between EG and estrogen concentration [26]. In addition, the peak time of estrogen and HG is not consistent - EG and HG are mostly pronounced in the I trimester, while estrogen level is maximum high in the III trimester [45]. Considering that the potential role of estrogen is controversial in high-quality studies, it is unlikely to play a role in the aetiology of HG.

Clinicians are well aware of the high functionality of the corpus luteum in the I trimester, which is associated with high progesterone concentration, and therefore postulate a link between high progesterone and HG [23]. This fact can be explained by the effect of progesterone on sphincters, particularly the relaxation of the lower oesophageal sphincter [23, 80]. However, M. F. Verberg et al. mentioned that some iatrogenic processes increase progesterone level but do not lead to an elevated incidence of HG, such as pregnancy during which progesterone is administered to support the luteal phase or pregnancy with multiple corpus luteum that resulted from controlled ovarian stimulation. This suggests that high levels of progesterone (endogenous or exogenous) as this may not cause HG [80].

However, the progesterone receptor gene has been linked to the occurrence of HG in a genome-wide association and replication study, providing evidence that the progesterone signalling pathway may be associated with HG without it abnormal level [20]. More comparative and molecular studies are needed to determine the role of progesterone in the genesis of EG and HG.

Serotonin plays its own role in the pathogenesis of vomiting through its effects on the CNS and digestive tract. Although A. Borgeat et al. found that pregnant women with EG and HG do not have high serum serotonin levels, the role of anti-serotonin agents in chemotherapy-induced vomiting and their efficacy in HG are two strong evidence factors that support this link [10].

In early pregnancy, physiological stimulation of the thyroid gland sometimes results in transient thyrotoxicosis. Biochemical hyperthyroidism (elevated free thyroxine level and/or suppressed thyroid-stimulating hormone) was diagnosed in 66.0% of patients with HG. Thyroid hormones may play an intermediary role in many complex mechanisms, and further research is needed to explore them.

An abnormal thyroid functional test does not require treatment with thyroid-stimulating agents and disappears as hyperemesis decreases. True thyrotoxicosis can occur in early pregnancy. Discriminating features to distinguish this from gestational hyperthyroidism include the presence of tremor, exophthalmos, goiter with bruit, and thyroid-stimulating antibodies [35]. R. Wilson et al. suggested that high concentration of thyroid hormones, thyroid antibodies, and high hCG level cannot be the cause of vomiting [83].

Some researchers consider TNF-α to be a factor in the pathogenesis of HG. Increased concentrations of free

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DNA in fetal cells were found in blood serum of pregnant women with this pathology, which led to an overactive immune response and trophoblast damage in the mother. It has been suggested that it is the overactive maternal immune system that causes HG [75]. TNF-α can affect trophoblast cells during early pregnancy to reduce hCG secretion [45].

To date, it is unclear whether high TNF-α level in patients with HG is the cause or consequence of excessive vomiting. However, since HG is a self-limiting condition, the elevation of these seemingly random immune factors may be a part of the compensatory response that limits its progression. Additional studies are unlikely to resolve these issues, and resources dedicated to elucidating the aetiology would be better spent elsewhere [80].

It is known that during pregnancy, the lower oesophageal sphincter relaxes due to increased levels of estrogen and progesterone. This leads to more frequent symptoms of gastroesophageal reflux (GER) during pregnancy. It should be recalled that one of the symptoms of GER is nausea. Studies investigating the association between GER and vomiting during pregnancy have reported conflicting results [35].

It was found that the majority of pregnant women with HG are seropositive for *H. pylori* infection, while there is no association between *H. pylori* seropositivity and the duration of HG symptoms. In 2018, A. Goymen et al. found that HG can lead to a significant increase in oxidative burden and some decrease in the antioxidant capacity of saliva. This may be the result of *H. pylori* infection, and such infection was more commonly diagnosed in women with poor oral hygiene. In general, *H. pylori* infection can exacerbate the symptoms of EG or HG, but it is unclear from studies whether eradication of *H. pylori* before pregnancy can significantly reduce the risk of HG [27].

Pregnant women with psychological disorders are prone to adverse health outcomes, including EG and HG [59]. As of today, 17 studies have found that adverse psychological factors are associated with this pregnancy pathology. The possible adverse psychological factors included depression, anxiety, mood disorders, and stress. A pattern was established whereby women with vomiting during pregnancy experienced a significant improvement in their general state following depression, anxiety and stress. By the III trimester, the level of psychological stress in women with HG was even lower than in the control group. This observation indicated that a significant portion of the psychological distress of HG is self-limiting [31].

Increased risk of pregnancy hyperemesis has been demonstrated among women whose family members also had pregnancy hyperemesis. Two genes, GDF15 and IGFBP7, are potentially associated with the development of pregnancy hyperemesis [35]. The history of HG is associated with an increased risk of recurrence in future pregnancies, which is important for risk assessment, patient counselling, and treatment.

In addition, several factors have been identified that may modify the risk of HG recurrence, including gestational age at diagnosis and the disease severity during the first pregnancy. The risk of recurrence was significantly higher during the second pregnancy for patients whose first pregnancy resulted in delivery at 32-36 weeks and ≥ 37 weeks' gestation [23].

According to the previous analysis by D. H. Konkov [2016], the risk factors for excessive vomiting in pregnant women include:

- weight loss before pregnancy;
- previous pregnancy complicated by hydatidiform mole (RR 3.3; 95% CI: 1.6-6.8);
- second pregnancy (RR 26.4; 95% CI: 24.2-28.7);
- hyperthyroidism (RR 4.5; 95% CI: 1.8-11.1);
- diabetes mellitus (RR 2.6; 95% CI: 1.5-4.7);
- mental disorders and diseases (RR 4.1; 95% CI: 3.0-5.7);
- gastrointestinal disorders (RR 1.5; 95% CI: 1.8-3.6);
- *H. pylori* infection (RR 3.32; 95% CI: 2.25-4.90);
- asthma (RR 1.5; 95% CI: 1.2-1.9).

There was also a definite association between HG and multiparity; pyelonephritis and other urinary tract infections; depression or anxiety; unplanned pregnancy; overweight; young age; allergic history; restrictive diet (e.g. lactose exclusion, vegetarianism, or nutritional deficiencies); financial and other situational stress; cultural isolation, distance from the country of origin and from a partner or family [1].

Differential diagnosis

The diagnosis of EG and HG is a clinical and predominantly a diagnosis of exclusion. The list of possible diagnoses in patients with similar symptoms is quite extensive. According to the Morgannwg University clinical guideline (2022) and the review by S. A. Lowe et al. (2022), the differential diagnosis should exclude the following diseases [49, 85]:

- irritable bowel syndrome;
- hepatitis;
- metabolic disorders (e.g., diabetic ketoacidosis, porphyria, Addison's disease);
- reflux oesophagitis;
- gastritis;
- inflammatory bowel disease;
- cholithiasis;
- gastroesophageal reflux;
- benign intracranial hypertension;
- peptic ulcer disease;
- hormone-dependent tumour of the pituitary gland;
- appendicitis;
- hyperparathyroidism;
- hyperthyroidism;

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- ovarian cyst torsion;
- pyelonephritis;
- malaria;
- intestinal obstruction;
- vestibular dysfunction.

Other obstetrical complications in the I trimester include ectopic pregnancy, which is more likely to include abdominal pain, syncope, or vaginal bleeding and also can be evaluated by obstetrical ultrasound examination and beta-hCG level.

The onset of nausea and vomiting after nine weeks should spark concern for alternative diagnoses. Preeclampsia, HELLP (haemolyses, elevated liver enzymes, and low platelets), and acute fatty liver of pregnancy occur during the late II or III trimester of pregnancy typically. Non-obstetrical causes for nausea and vomiting can also occur during pregnancy and should always remain on the differential, keeping in mind that pregnant patients are considered to be at higher risk of blood clotting; therefore, diagnoses that lead to ischaemia or thrombus formation may be more common during pregnancy.

Gastrointestinal causes such as gastroenteritis, small bowel obstruction, gastroparesis, peptic ulcer disease, cholecystitis, pancreatitis, hepatitis, and appendicitis should be considered. Pyelonephritis, urinary tract infections, renal stones, and ovarian torsion may also include vomiting. Metabolic disorders such as diabetic ketoacidosis, hyperthyroidism, and hyperparathyroidism may also have similar symptoms. Neurologic disorders such as migraine, intracranial haemorrhage, pseudotumor cerebri, and venous sinus thrombosis can also cause vomiting but are likely to have associated headaches or neurological deficits. Psychiatric disorders, such as anxiety and depression, can also lead to vomiting, toxic ingestion, and myocardial ischaemia [35].

Long-term use of cannabis can contribute to the onset of cyclic vomiting, known as cannabinoid hyperemesis syndrome (CHS) [5]. The description of this syndrome is relatively recent, and CHS is still not well understood or properly recognised [63, 69]. CHS is a recurrent but intermittent syndrome, primarily among some regular consumers of cannabis with high frequency and dose. There are three phases:

1) Prodromal—symptoms include nausea, especially early-morning, abdominal pain, and fear of vomiting but normal eating patterns.
2) Hyperemetic—symptoms include intense, persistent, recurrent, or cyclic vomiting, frequently accompanied by dehydration, with the sequelae lasting 1 to 2 days in many cases but up to 7 to 10 days in other cases.
3) Recovery—complete resolution of symptoms and a return to normal eating behaviours. [24].

Until 2015, CHS, which was considered relatively rare, was diagnosed in about 6% of patients who admitted to the emergency department with recurrent vomiting. However, the number of diagnosed cases is increasing in countries with legalised cannabis use due to the significant similarities between prodromal symptoms and common «morning sickness», the relatively low prevalence of HG, and the reluctance of pregnant women to report cannabis use. That is why CHS can be easily confused with nausea and vomiting of other aetiologies, hyperemesis, and cyclic vomiting syndrome [41].

Other clinicians and researchers have recommended that CHS should be considered in the differential diagnosis of atypical or resistant HG [41]. Today, CHS is included in the American Society of Obstetricians and Gynaecologists' recommended differential diagnosis of HG as "Miscellaneous conditions: Drug Toxicity or Intolerance" [32, 33].

Table 1

Clinical classification of vomiting in pregnant women [1]

Symptom	Severity of vomiting		
	Mild	Moderate	Severe
Frequency of vomiting per day	3-5 times	6-10 times	11-15 times and more often
Pulse rate, per 1 min	80-90	90-100	> 100
Systolic blood pressure, mm Hg	120-110	110-100	< 100
Weight loss per week, kg	1-3 (up to 5% of the initial weight)	3-5 (1-1.5 kg per week, 6-10% of the initial weight)	More than 5 kg (2-3 kg per week, >10% of initial weight)
Increased body temperature to subfebrile level	Not observed	Observed rarely	Observed frequently (in 35% of patients)
Jaundice of sclerae and skin	Absent	In 5-7% of patients	In 20-30% of patients
Hyperbilirubinaemia	Absent	21-40 μmol/L	21-60 μmol/L
Skin dryness	+	++	+++
Stools	Every day	Once every 2-3 days	Delayed voiding
Diuresis, mL	>800	800-700	< 700
Ketonuria	-/+	+, ++, +++ (occasionally in 20-30% of patients)	+++, ++++ (in 70-100% of patients)

Note. +, ++, +++ = symptom severity.

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Table 2

Modified PUQE-24 score for assessing the severity of nausea and vomiting in pregnant women [84]

How long have you experienced nausea, discomfort or pain in the stomach in the last 24 hours?				
None	≥ 1 h	2-3 h	4-6 h	> 6 h
1 point	2 points	3 points	4 points	5 points
Have you vomited and how many times in the last 24 hours?				
None	1-2 times	3-4 times	5-6 times	> 6 times
1 point	2 points	3 points	4 points	5 points
How many times have you had an urge to vomit that did not lead to vomiting?				
None	1-2 times	3-4 times	5-6 times	> 6 times
1 point	2 points	3 points	4 points	5 points
Interpretation: mild degree – ≤ 6 points; moderate degree – 7-12 points; severe degree - ≥ 13 points.				

Screening in early pregnancy for cannabis use should be introduced and implemented in an evidence-based, non-judgemental manner, explaining that clinicians are aware of people's beliefs about cannabis as a natural anti-emetic and the paradoxical effects experienced by pregnant women. Furthermore, if symptoms can be partly caused by cannabis use, effective treatment will be slightly different. Valid screening tools with good sensitivity and appropriate predictive value are available for pregnant women, if standardised tools are needed [16].

Classification and diagnostic tests

Criteria for diagnosis include vomiting that causes significant dehydration (as evidenced by ketonuria or electrolyte imbalance) and weight loss (the most common marker for this is a loss of at least 5% of the patient's body weight before pregnancy) during pregnancy, without any other underlying pathological cause of vomiting. Significant abdominal or pelvic tenderness or vaginal bleeding should prompt investigation for alternative diagnoses.

The clinical qualification of EG and HG is rather conditional and subjective, difficult to interpret and may be of limited use in practice (Table 1).

The modified PUQE-24 score was developed for use during pregnancy to assess the severity of EG and HG. It is based on the PUQE-24 score, which takes into account three parameters - nausea, vomiting and retching - that further care is provided (Table 2). This scale can also be used to assess the patient's condition over the course of treatment.

According to the Australian Society of Obstetricians and Gynaecologists clinical practice guideline, nausea, vomiting and/or retching which are caused by pregnancy without an alternative diagnosis on the PUQE-24 scale are divided according to severity: mild degree = 4-6 points; moderate degree = 7-12 points and severe ≥ 13 points [48].

Patients with mild to moderate nausea and vomiting during pregnancy (PUQE-24 score ≤ 12) whose symptoms are not suspicious for an HG or other diagnosis do not require further investigation. The history taking and physical examination should aim to rule out alternative diagnoses. The physical examination should include assessment of body temperature, body weight, abdominal palpation for tenderness and signs of peritonitis; neck stiffness and signs of increased intracranial pressure if the history suggests a central nervous system cause for the symptoms.

Signs that support the diagnosis of dehydration include decreased skin turgor, dry mucous membranes, decreased urine output, decreased urine concentration, and a postural decreased blood pressure [48]. Assessment should include a urinalysis to check for ketonuria and specific gravity in addition to a general blood test and electrolyte count.

Elevated haemoglobin or haematocrit levels may be a result of haemoconcentration in the presence of dehydration. Significant dehydration can lead to acute kidney damage, as evidenced by increased serum creatinine, blood urea nitrogen and decreased glomerular filtration rate. Potassium, calcium, magnesium, sodium, and bicarbonate levels may be affected by prolonged vomiting and reduced oral fluid intake. Thyroid, lipase, and liver function tests may also be completed to determine alternative diagnoses [35].

In women with severe EG (PUQE-24 score ≥ 13) or suspected HG, the following tests should be performed at the first visit to a doctor:

1. Serum sodium, potassium, chloride, bicarbonate, magnesium, urea and creatinine
2. Bilirubin, alanine transaminase, aspartate aminotransferase, albumin
3. Obstetric ultrasound examination to exclude multiple pregnancy or gestational trophoblastic disease
4. Tests to exclude alternative diagnoses (serum hCG as a baseline, if hydatidiform mole is suspected on ultrasound examination , etc.)
5. Thyroid-stimulating hormone (TSH), if indicated [38].

Electrolytes and renal function

Pregnant women with HG often have hyponatraemia, hypokalaemia, hypochloraemia, hypomagnesaemia and low serum urea levels with metabolic hypochloraemic alkalosis. In severe cases, metabolic acidaemia may develop [15, 66]. Increased serum creatinine (>70 μmol/L) indicate significant dehydration. Starvation ketoacidosis can rarely occur, leading to significant metabolic disturbance.

- In patients who do not require hospitalisation or infusion therapy, electrolyte levels should be repeated only if their condition worsens.
- For women who require repeated infusion therapy or hospitalisation, electrolyte levels should be measured daily or less frequently if stable after starting therapy.
- Calcium (Ca) - hypercalcaemia is a rare but potentially treatable cause of vomiting.
- Women with diabetes mellitus or other serious medical conditions need more frequent electrolyte monitoring (at least daily).

Liver function tests

- Liver enzyme levels are elevated in 15-50% of patients with HG, but are usually less than four times the upper limit of normal [25].
- Liver dysfunction most commonly involves mild to moderate elevations of transaminases (>two to three times the local reference range for pregnancy), but elevated bilirubin level may also be present, although it is usually lower [25].
- Liver impairment usually resolves rapidly with improvement of EG and HG symptoms [48].

If liver enzyme dysfunction is 4 times the upper limit of normal for pregnancy, further investigations should be considered.

Thyroid function tests

- Women with EG without the diagnostic criteria for HG do not need TSH measurement.
- TSH should be determined in women with treatment-refractory EG or HG or with milder symptoms, who have signs and/or symptoms of thyrotoxicosis.

Imaging studies

- An ultrasound obstetric examination should be performed for diagnosis to rule out multiple pregnancy, ectopic pregnancy and gestational trophoblastic disease, if it has not already done.
- Magnetic resonance imaging can be used to evaluate alternative diagnoses, such as a hormone-dependent pituitary tumour [35, 49].

Tactics of medical staff and non-pharmacological prevention

Early gestosis is such a common problem in early pregnancy that all healthcare professionals, including midwives, general practitioners, and obstetricians and gynaecologists, should be well trained to care for the majority of women with mild to moderate symptoms (PUQE-24 score < 12). The women often consult with pharmacists who can be an important source of information and advice on preventive treatment [49].

A detailed history taking in women with suspected or confirmed EG and HG should include pregnancy status, estimated gestational age, history of complications in previous pregnancies, frequency and severity of nausea and vomiting, any interventions attempted to treat their symptoms, and the results of attempted interventions. The physical examination should include blood pressure, heart rate, dry mucous membranes, capillary refill and skin turgor. The patient's body weight should be measured to compare with previous and future body weight [35].

A study of the value of professional support (including individual health education through the provision of an information booklet and support phone calls) for women with EG and HG demonstrated a reduction in symptom severity and distress and a significant improvement in quality of life ($p<0.05$) [46]. Although there was no significant difference between the two groups in terms of weight gain at 4 weeks of gestation, attentive empathic care is an important aspect of holistic treatment.

Clinical assessment and care of women with severe EG or HG (PUQE-24 score ≥ 13) should be carried out by clinicians who are experienced in recognising the signs and symptoms of HG and in effectively managing this condition. These clinicians should be identified in each facility where pregnant women are cared for. Depending on local resources, this may be an obstetrician, a physician (internist, emergency physician or gastroenterologist) or a general practitioner [48].

A nutritionist should also consult all women who require inpatient care, as well as women with prolonged symptoms of ET, especially if there are signs of malnutrition or undernutrition. Due to resource constraints, access to an experienced clinician may be limited, so experienced practitioners should be accessed through an appropriate referral pathway (e.g., a tertiary care facility) or telemedicine [48].

Most women with a PUQE-24 score <13 can be managed in outpatient department. In women with severe EG or HG (PUQE-24 score ≥13), medical care alone may not be sufficient. Women with type 1 diabetes and other high-risk conditions (e.g., short bowel syndrome) or those requiring continuous use of essential oral medications (e.g., severe epilepsy, post-transplant patients) should be hospitalised at least for initial treatment and until their condition stabilises [66].

Whenever possible, outpatient day care and home-based services should be used for women who require infusion therapy and parenteral antiemetics if they are unable to take them orally in an outpatient department [48]. Outpatient EG and HG services provide quick and easy access to women with severe symptoms and have

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the potential to promote self-referral [37]. The ability to access outpatient services instead of inpatient hospitalisation is useful for minimising disruption and maintaining a supportive family environment.

A study found that outpatient care was associated with symptom improvement in 89% of women. The parameters of persons who did not receive outpatient care in this study included a higher mean PUQE-24 score at the start of outpatient care, earlier gestational age at the start of HG, and the need for additional parenteral fluids during outpatient care [49].

A randomised trial of 98 women with EG demonstrated that outpatient day treatment according to protocols with a switch to intravenous solutions and antiemetic therapy reduced the frequency of hospitalisation and was satisfactory for women enrolled in the programme [55].

A subsequent cost-effectiveness analysis confirmed the cost-effectiveness of day care compared to inpatient care [49]. In the absence of access to inpatient day care and home-based care, alternative care options should be considered. This may include: parenteral rehydration therapy and/or antiemetics in local hospital emergency departments; general practice/family medicine centres; private infusion centres [48].

During outpatient treatment, women need regular examination, at least every 1-2 weeks, by their primary clinician to ensure that the prescribed therapy is appropriately adjusted and optimised. Midwife-led outpatient care was associated with less hours of hospitalisation than usual hospitalisation (mean difference [MD] 33.20, 95% CI 46.91 to 19.49), with no difference in the quantitative assessment of vomiting and nausea (PUQE-24), decision to interrupt pregnancy, miscarriage rate, or cases of small for gestational age fetuses [8].

For women with severe HG, outpatient treatment may not be sufficient and hospitalisation may be needed. A recent study documented that 38% of women were readmitted to hospital on average 11.2 days after outpatient care [60]. Three factors were identified as predictive of readmission: gestational age < 9 weeks, duration of hospitalisation of more than 2 days, and HG during a previous pregnancy.

Inpatient treatment is necessary for women with:

- severe electrolyte disturbances, e.g. potassium < 3.0 mmol/L;
- significant renal impairment or acute kidney injury: creatinine > 90 mmol/L;
- comorbidities, such as type 1 diabetes mellitus, poorly controlled epilepsy, post-transplantation, or pregnant patients requiring significant immunosuppression;
- malnutrition/persistent significant weight loss despite treatment or diet, ketoacidosis;
- comorbidities requiring inpatient treatment, such as infection.

Hospital discharge is indicated when the patient is able to receive oral pharmacotherapy, oral nutrition and tolerates oral hydration [48].

In all cases, the clinician should provide the patient and family with a clearly documented plan for ongoing treatment, including details of therapy, arrangements for repeated clinical evaluation, and measures for ongoing prenatal care [49].

Although pregnancy vomiting is common, not all women ask for help. A web-based, cross-sectional study received responses from 9113 women across Europe, North America, and Australia on the frequency of nausea and factors associated with EG and HG treatment [29]. Among these women, 17.9% used "conventional medications" and 8.3% used herbs. Among Australian respondents, the figures were 24.0% and 21.7%, respectively.

In a recent Australian study, only 39.0% of women used some form of treatment for pregnancy vomiting, of which 15.0% used pharmacotherapy, with the majority using over-the-counter treatments such as vitamin B6, ginger, and "natural remedies" [48].

Multiple systematic reviews have attempted to assess the heterogeneous and limited high-level evidence on the efficacy and safety of the EG and HG treatment [8, 54, 57]. Adverse treatment reactions, including bowel distress, gastroesophageal reflux, sedation, symptoms of uncontrollable urination, and vaginal bleeding, abdominal pain, and miscarriage, should be considered when evaluating treatment outcomes, the dynamics of EG and HG resolution, and the subsequent impact on perinatal outcomes.

Since nausea and vomiting are very common during pregnancy, the following non-pharmacological preventive strategies are suggested.

Rest

The first trimester of pregnancy is often associated with fatigue, while pregnancy is often not publicly disclosed. In a prospective study of more than 7000 Dutch women, 44.0% of them described daily fatigue, which was associated with an increased incidence of nausea during pregnancy [6]. Interventions to reduce nausea and fatigue include modifying work routines, exercise, naps, and earlier bedtimes, but there is a lack of evidence on the efficacy of these methods [13, 48].

Diet

Although large observational studies have demonstrated changes in the quantity and quality of the diet of women with EG and HG, there is no evidence that this is effective [17]. An ecological study in 21 countries reported higher rates of nausea and vomiting with higher intakes of meat, milk and eggs, and lower intakes of grains and legumes [14]. However, none of these studies evaluated dietary effects before pregnancy for comparison. Prior to pregnancy, a diet with higher daily intake of saturated fat increased the incidence of hospitalisation for pregnancy-

related vomiting in American women [48]. Vitamin intake has been associated with a reduced risk of vomiting in pregnant patients, especially in HG [36, 49].

Standard recommendations include more frequent consumption of small, low-fat meals, preferably in the first half of the day, avoidance of dairy products and iron supplements, avoidance of nausea-inducing odours, and replacement of prenatal vitamins with folic acid only [12]. One study showed that protein foods can selectively reduce nausea and gastric slow arrhythmia in the I trimester of pregnancy [48].

Ginger (250 mg orally 4 times daily) should be considered if necessary [35]. Preventive ginger therapy is a simple, affordable, convenient and effective method of treating nausea and vomiting during pregnancy. Ginger stimulates the movement of the digestive tract, the outflow of saliva, bile and gastric secretion. Ginger extracts not only inhibit the growth of certain strains of *H. pylori*, but one of its components has also been found to have similar activity to the 5-HT3-ondansetron antagonist in reducing nausea and vomiting during pregnancy [51]. The safe use of 1000 mg of ginger per day for 4 days can relieve symptoms of nausea and vomiting in pregnant women, an effect that may be due to its anticholinergic and antihistamine properties [77].

In a comparative study involving 70 patients, T. Vutyavanich et al. (2001) compared changes in the degree of nausea between the two groups using the Fisher's exact test and demonstrated that ginger can effectively relieve the severity of nausea and vomiting during pregnancy without significant adverse effects [81]. In addition, F. Saberi et al. (2014) also found in a controlled study that ginger effectively relieves mild to moderate nausea and vomiting in pregnant women up to 16 weeks of gestation [70].

A Cochrane meta-analysis by R. C. Boelig et al. (2018) reported that the use of ginger to reduce the severity of nausea and vomiting during the first three months of gestation was safe and better than placebo and pyridoxine [8]. However, Y. Hu et al. (2018) reported that ginger may slightly reduce the severity of general vomiting symptoms in pregnant women, but it had no significant effect on vomiting compared to placebo [34].

Strikingly, a survey of women with EG and HG found that 87% of respondents had tried ginger for symptom relief, and 88% of them reported that it was completely ineffective; 51% of respondents reported that their symptoms worsened, and 82% reported that ginger use caused their mood to worsen, such as feelings of anger, lack of effect, isolation, guilt, and feelings of being misunderstood. In addition, 79% of women who were recommended to use ginger by a healthcare provider reported that it harmed their trust and confidence in their doctor [18]. Therefore, more researches are needed to demonstrate the efficacy of ginger in the treatment of nausea and vomiting during pregnancy.

In addition, due to the lack of safety studies at doses >1000 mg/day and due to potential suppressive effects on platelet function, ginger is not recommended for pregnant women receiving anticoagulant therapy [45].

Acupuncture/acupressure

There are very few studies available in English-language journals on the use of traditional acupuncture for the treatment of EG and HG. Only two studies compared acupuncture with sham or placebo treatment, and neither found clinically significant symptom relief [48]. No serious adverse events have been reported from the use of acupuncture.

Stimulation of the P6 point (Nei guan) on the wrist has been used by acupuncturists for thousands of years to treat nausea and vomiting for various reasons. Acupressure bracelets are commonly used by women who experience nausea in early pregnancy. However, a 2015 Cochrane review of 6 studies comparing acupressure with placebo showed no overall significant reduction in symptoms in women [54].

Recently, a Malaysian study compared two groups of 60 women who were hospitalised for moderate hyperemesis. They were randomised to wear acupressure dressings or placebo dressings for at least 12 hours a day for three days [4]. This study demonstrated a significant improvement in PUQE-24 scores on day 3 in those randomised to the treatment group (mean ± standard deviation: 4.40±0.63 vs. 7.10±1.61; $p<0.001$). The authors emphasised the importance of wearing acupressure tape for at least 12 hours a day. Of interest, a higher percentage of women in the placebo group were satisfied with the treatment (85%) than in the treatment group (72%; $p<0.8$) [48].

The mechanism of PC-6 acupressure for EG and HG is unclear, and most women and healthcare professionals remain sceptical about its benefits. A. Heazell et al. (2006) noted that P6 acupressure did not reduce the need for antiemetics, the number of infusions, or the average length of hospitalisation compared to placebo [28].

C. Smith et al. (2002) conducted a controlled trial using traditional acupuncture with a group of acupoints in the mid- and upper abdomen, PC-6 acupuncture, and no acupuncture, observing the severity of nausea and vomiting time. After 4 weeks, their findings were that PC-6 acupuncture was more effective in reducing nausea and vomiting in women than traditional acupuncture or no acupuncture [73].

Similarly, K. Sridharan et al. (2020) also found that acupuncture reduced nausea and vomiting in pregnant women [74]. Additionally, in a comparative study involving 90 patients, Z. N. Mao et al. (2009) found that after 7 days of treatment, the overall efficacy in the acupuncture group was 96.7%, and the experimental results demonstrated that acupuncture was a rapid, obvious, and side-effect-free strategy for the treatment of vomiting in pregnancy [52].

The PROSPERO meta-analysis included 16 studies covering 1043 pregnancies. Compared with convention-

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al treatment, acupuncture was significantly more effective (OR 8.11; 95% CI: 5.29~12.43; p<0.00001), it had more urinary ketone conversion rate (OR 1.36; 95% CI: 1.15~1.60; p=0.0003), rate of relief from nausea and vomiting (OR 26.44; 95% CI: 3.54~197.31; p=0.001) and a relatively higher rate of improvement in food intake (RR 1.17; 95% CI: 1.01~1.36; p=0.04). The use of acupuncture also reduced hospitalisation time and the rate of abortion and adverse events.

However, there was no statistical variation in the reduction of nausea, vomiting, and symptoms of fatigue, reduction of recurrence, or normalisation of serum potassium levels [50]. However, in the absence of high-quality randomised trials, the benefits of acupuncture in the treatment of nausea and vomiting in early pregnancy remain sceptical. According to a meta-analysis by S. Liu et al. (2022), neither acupuncture nor acupressure was effective in treating women with nausea and vomiting during pregnancy [45].

Hypnosis

A review of 45 studies on the use of hypnosis for the prevention and treatment of EG found no high-quality clinical evidence of its efficacy [56]. The results of the study by S. E. Ozgunay et al. (2022) demonstrated that the adjunctive use of hypnotherapy in patients diagnosed with HG significantly reduced the severity of nausea and decreased the frequency of vomiting compared to conventional treatment alone. It was also found that hospital stays were shorter in the treatment group compared to the control group. These findings are encouraging and suggest that it is feasible and potentially beneficial to include additional hypnotherapy in the treatment of HG [62].

The topic of optimising pharmacological treatment, especially infusion therapy, will be covered in our next analytical review.

Immediate and long-term effects of vomiting in pregnancy

Nausea and vomiting is a common condition in pregnant women, ranging from mild to moderate nausea and vomiting, HG is a pathological form that causes severe clinical consequences. Treatment of EG and HG consists mainly of symptomatic therapy, ranging from dietary changes and oral antiemetics to hospitalisation with infusion therapy and intravenous antiemetics. Most studies indicate that pregnancy vomiting is not harmful to the fetus, but can significantly impair the patient's quality of life during pregnancy [45].

Most women with HG are at increased risk of adverse pregnancy outcomes, such as small for gestational age fetuses, low birth weight, preterm birth, and low 5-minute Apgar scores [40].

Uncontrolled HG is associated with an increase in adverse maternal and fetal outcomes, including Wernicke's encephalopathy (vitamin B1 deficiency), haemorrhagic diathesis (vitamin K deficiency), acute kidney injury and oesophageal rupture, as well as significant impact on emotional and psychological well-being. HG can also cause placental dysfunction with an increased risk of newborns who are small for gestational age (OR 1.42; 95% CI: 1.27-1.58), preterm birth (OR 1.32, 95% CI: 1.04-1.68), preterm birth and pre-eclampsia (OR 2.09, 95% CI: 1.38-3.16) and placental abruption (OR 3.07, 95% CI: 1.88-5.00) [49].

Neurological complications. The search identified 11 articles on severe neurological complications of HG, of which four articles addressed stroke, two articles focused on seizures, three publications - on cerebral venous thrombosis (CVT), two articles related to Wernicke encephalopathy (WE), and two articles focused on WE alone [65].

Of the 1,408,015 births, 183 cases of perinatal stroke and 170 cases of peripartum cerebral venous sinus thrombosis (CVST) were identified. The risk of stroke and CVT in patients with HG was statistically significant (p=0.009) [43]. It is important to note that there is limited evidence regarding the risk of seizures in patients with HG. In addition, although brain damage is thought to be the cause of seizures, other factors, including blood pressure fluctuations, metabolic disorders, and infections, may also contribute to this risk [7].

CVT is one of the rarest but potentially fatal complications of HG. It is mainly caused by the following conditions: rapid correction of hyponatraemia, alcoholism, malnutrition, burns, hypokalaemia, psychogenic polydipsia (patients with schizophrenia), liver cirrhosis, and severe electrolyte and acid-base disorders [72].

WE is a type of encephalopathy caused by vitamin B1 deficiency. This disease is clinically characterised by the classic triad of vision problems, disorientation, and balance disorders. Epidemiological studies are rare and unreliable, as >80% of patients with WE are either undiagnosed or misdiagnosed, making it impossible to calculate morbidity and mortality rates. WE is the most common neurological complication of HG, reported in more than 70 articles over the past 60 years. These papers are not included in the current review, as they were all case reports. Today, WE can be easily diagnosed, treated, prevented, and even cured in severe cases thanks to new pharmacological agents and individual therapy [61].

Cardiovascular complications. There are limited literature data on cardiovascular complications due to HG, and most published articles describe case reports. The search strategy identified 7 articles with information on cardiovascular complications in HG: three case reports related to ventricular arrhythmias. All of them discussed the consequences of electrolyte imbalance in the blood serum, mainly hypokalaemia, including: one report described a case of *Q-T* interval prolongation and two cases included ventricular tachycardia; one population-based cohort study assessing the risk of pre-eclampsia; one nationwide cohort study assessing the subsequent long-term risk of maternal cardiovascular morbidity; and one case of significant blood pressure fluctuations [65].

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Q-T interval prolongation with subsequent malignant ventricular arrhythmias is a condition caused by electrolyte imbalances in the blood serum (mainly hypokalaemia, but also hypomagnesaemia and hypocalcaemia) that can be treated with antiemetics. Nausea is treated with antiemetics, which can further prolong the *Q-T* interval and cause malignant ventricular arrhythmias [58].

The association between HG and pre-eclampsia was discussed in the study by M. Bolin [9], who evaluated the possible association between HG during the I or II trimester of pregnancy and placental dysfunction disorders, including pre-eclampsia, placental abruption, and stillbirth. Over 13 years, 1,156,050 pregnancies were included. The results demonstrated that women with HG had a higher risk of pre-eclampsia in the I trimester of pregnancy compared to that observed in persons with HG in the II trimester of pregnancy, who demonstrated a more than 2-fold increase in the risk of pre-eclampsia (OR 2.09; 95% CI: 1.38-3.16).

The Norwegian cohort study included an analysis of data from patients with and without HG for the period from 1967 to 2002. These cases were followed up from 1994 to 2009, and the following cardiovascular outcomes were reported: non-fatal stroke, myocardial infarction or angina, and cardiovascular death. The authors emphasised that the incidence of HG in the cohort of 989,473 women was 1.3%. There was no association between HG and the risk of fatal or non-fatal cardiovascular events (adjusted hazard ratio (HR) 1.08; 95% CI: 0.99-1.18). Only the risk of hospitalisation for angina was higher in patients with HG (HR 1.28; 95% CI 1.15-1.44). The risk of death as a result of cardiovascular pathology was not significantly different in patients with and without HG (HR 0.73; 95% CI: 0.59-0.91) [22].

Thoracic complications. This search strategy yielded 8 articles related to thoracic complications of HG, most of which included case reports. The selected articles provided evidence for pneumothorax, pneumomediastinum, diaphragmatic rupture, and venous thromboembolism [65].

Systemic complications. The search strategy yielded 17 articles related to systemic complications of HG, of which two articles addressed rhabdomyolysis, one article - porphyria, three - electrolyte imbalance, seven - vitamin K deficiency, two - endocrine complications, and two - infectious complications [65]. HG can lead to hypovolaemia and electrolyte imbalance, which in turn causes rhabdomyolysis. A total of two reports describe this complication in the I trimester of pregnancy [44].

Hyponatraemia, hypokalaemia, hypochloraemia, hypophosphataemia and dehydration caused by HG can affect other parameters including *QRS* prolongation, increased haematocrit, hepatic cholestasis and cytolysis with elevated transaminases, hepatic steatosis and hypoalbuminemia [38].

Hypokalaemia is usually caused by nutrient deficiencies as a result of electrolyte loss, decreased extracellular fluid volume, and activation of the renin-angiotensin-aldosterone axis [39]. The authors of the above study reported a case of nephrogenic diabetes insipidus (characterised by polyuria with impaired urine concentration) and rhabdomyolysis (with increased creatine kinase levels) as a consequence of electrolyte imbalance with hypokalaemia observed during prolonged HG.

Vitamin K deficiency is rarely associated with HG but can cause serious complications. A. S. Lane et al. (2015) reported that embryopathy with nasal hypoplasia was causally associated with HG [42]. In addition, D. Shigemi et al. (2015) reported a case of HG associated with fetal intracranial haemorrhage [71]. Vitamin K deficiency is a complication of malnutrition and liver dysfunction associated with prolonged HG. In extremely rare cases, vitamin K deficiency can cause coagulopathy and intracranial haemorrhage in the fetus, leading to hydrocephalus and miscarriage.

Several reports have suggested a possible association between HG and severe fetal complications, including gray matter heterotopia associated with seizures and various types of bone dysplasia, such as brachytelephalangic chondrodysplasia punctata, which corresponds to the Binder phenotype [65]. Transient gestational thyrotoxicosis in HG is very common with an incidence of ~48%, and its severity correlates with serum hCG level [76].

In summary, life-threatening complications are extremely rare in HG. The most frequent severe complications are encephalopathy, electrolyte imbalance, and vitamin K deficiency. The low mortality rate of HG patients over the past decade is due to the high efficiency of current therapies, allowing individual treatment of each complication using modern guidelines.

The following systematic review (2021) aimed to synthesise the available evidence from observational studies on the impact of HG on neonatal outcomes. The review was conducted in accordance with PRISMA guidelines, and the quality of the included studies was assessed using the Newcastle-Ottawa scale. The results of this systematic review indicated that the current evidence is contradictory regarding the association between HG and adverse neonatal outcomes. Most studies that examined the association between HG and preterm birth found no statistically significant differences. One study found that preterm birth rates were similar between groups, and three studies found a positive association between HG and preterm birth [79].

Women with HG had a higher risk of developing endodermal cancer compared to women without the above mentioned pregnancy pathology - 5.8 vs. 4.8 per 10,000 person-years (RR 1.36; 95% CI: 1.17-1.57), but not mesodermal or ectodermal cancer. HG with a metabolic disorder was more strongly associated with endodermal germ cell cancer (RR 1.97; 95% CI: 1.51-2.58), specifically bladder cancer (HR 2.49; 95% CI: 1.37-4.53), colorectal cancer (RR 1.41; 95% CI: 1.08-1.84) and thyroid cancer (RR 1.43; 95% CI: 1.09-1.64) [53].

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CONCLUSIONS

1. Nausea and vomiting of pregnancy are observed in approximately 80% of women and are characterised by varying severity of symptoms, which usually develop in the 5th-6th week of pregnancy.

2. The diagnosis of hyperemesis gravidarum is made by excluding other causes. It is characterised by severe, prolonged nausea and repeated vomiting, leading to dehydration, electrolyte imbalance and very often to hospitalisation.

3. Women who experience nausea and vomiting for the first time after 10 weeks of gestation are likely to have an alternative diagnosis to pregnancy nausea/vomiting.

4. An outpatient management strategy should be developed for women with diabetes mellitus, hyper/hypothyroidism, epilepsy or other existing conditions that may be adversely affected by nausea and vomiting. Women with diabetes should be detailed monitored, since dehydration increases the risk of diabetic ketoacidosis.

5. The severity of nausea, vomiting and excessive vomiting in pregnant women should be assessed using the modified 24-hour PUQE-24 (Unique Quantification of Emesis and Nausea in Pregnancy) score.

6. There is no evidence to support the efficacy of dietary restrictions in relieving symptoms, that is why patients are advised to avoid personal nausea triggers.

7. When planning a pregnancy and in early gestation, all women should be asked about their drug use, including marijuana and other cannabinoids or medications used for non-medical reasons.

8. Counselling should be offered to all pregnant women with vomiting, emphasising the self-limiting nature of the condition.

9. Women with hyperemesis gravidarum are at risk of developing endodermal cancer in the future.

Conflict of interest. The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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