The modern aspects of the optimal therapeutic strategy of hyperemesis gravidarum

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Although, nausea and vomiting in early pregnancy is very common, affecting approximately 80% of pregnancies, hyperemesis gravidarum (HG) is a severe form that complicates up to 2.2% of pregnancies. HG is one of the most common indications for hospitalization during pregnancy. In addition to the insufficient nutrition both for the mother and fetus, the severity of HG symptoms causes a serious psychosocial stress, which leads to depression, anxiety and even the development of perinatal pathology. The aim of this meta-analysis was to study available randomized controlled trials about therapeutic strategies by HG, their evaluation based on both subjective and objective measures of efficacy, maternal and fetal/neonatal safety, and economic costs.
A systematic data search was conducted using the databases MEDLINE, ISI Web of Science, PubMed, Scopus, Google Scholar, Cochrane Database of Systematic Reviews and publications in professional editions of Ukraine for 2013–2023. The search was conducted using the following keywords: pregnancy, nausea and vomiting of pregnant women, excessive vomiting of pregnancy, hyperemesis, antiemetic therapy during pregnancy, infusion therapy and the safety profile of medications prescribed during pregnancy in various combinations.
The main outcome was: the effectiveness of therapeutic strategies (reduction or stopping nausea/vomiting); detailing by safety profile of antiemetic drugs; optimization of infusion therapy; additional clinical strategies that help to improve the quality of care for pregnant women; adverse effects and side effects of drugs for HG for the mother/fetus/newborn.
The results presented in this meta-analysis can be used in the creation of a national clinical guideline, protocol, consensus or clinical recommendations regarding the clinical management of hyperemesis gravidarum.
Keywords: *pregnancy, early gestosis, hyperemesis gravidarum, fetus, PUQE-24, dehydration, ketonuria, antiemetic therapy, infusion therapy, xylitol, perinatal pathology, gastroesophageal reflux, acid-suppressive therapy, parenteral therapy.*

Сучасні аспекти оптимальної терапевтичної стратегії надмірного блювання вагітних

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Хоча нудота та блювання на ранніх термінах вагітності є дуже поширеними, обтяжуючи приблизно 80% вагітностей, тяжка їхня форма – надмірне блювання вагітних (НБВ) – ускладнює до 2,2% вагітностей. НБВ – це одне з найпоширеніших показань до госпіталізації під час вагітності. Окрім недостатнього харчування як матері, так й плода, тяжким наслідком НБВ є серйозне психосоціальне навантаження, що призводить до депресії, тривожності та навіть до розвитку перинатальної патології.
Метою цього мета-аналізу є вивчення наявних рандомізованих контрольованих досліджень щодо терапевтичних стратегій при НБВ, їхнє оцінювання на підставі як суб'єктивних, так і об'єктивних показників ефективності, безпеки для матері та плода/новонародженого, а також економічних витрат.
Проведено систематичний пошук даних по базах MEDLINE, ISI Web of Science, PubMed, Scopus, Google Scholar, Cochrane Database of Systematic Reviews та публікацій у фахових виданнях України за 2013–2023 рр. Пошук проводили за такими ключовими словами: вагітність, нудота та блювання вагітних, надмірне блювання вагітних, гіперемезис, антиеметична терапія під час вагітності, інфузійна терапія та профіль безпеки медикаментів, призначених під час вагітності у різних комбінаціях.
За основний результат прийнято: ефективність терапевтичних стратегій (зменшення або припинення нудоти/блювання); деталізація за профілем безпеки протиблювотних препаратів; оптимізація інфузійної терапії; додаткові клінічні стратегії, що допомагають підвищити якість надання допомоги вагітним; несприятливі наслідки та побічні ефекти препаратів, що використовують для лікування НБВ, для матері та плода/новонародженого.
Представлені у даному мета-аналізі результати можуть бути використані при створенні національної клінічної настанови, протоколу, консенсусу або клінічних рекомендацій стосовно клінічного менеджменту НБВ.
Ключові слова: *вагітність, ранній токсикоз, надмірне блювання вагітних, плід, PUQE-24, зневоднення, кетонурія, антиеметична терапія, інфузійна терапія, ксилітол, перинатальна патологія, гастроезофагеальний рефлюкс, кислотосупресивна терапія, парентеральна терапія.*

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Nausea and vomiting during pregnancy, or early gestosis (EG), affects approximately 80% of pregnant women and is characterised by varying degrees of symptoms that usually develop in the 5th-6th week of pregnancy, in most cases resolving by the end of the I trimester [2, 4, 41]. Numerous studies have shown that mild to moderate forms of EG are associated with more favourable fetal outcomes compared to women who do not have EG symptoms: Lower rates of miscarriage, preterm birth, stillbirth and various malformations have been reported [4, 5, 8].

Hyperemesis gravidarum (HG) is a severe form of EG and is observed in 0.3-2.3% of all pregnant women [61]. There is no universally accepted definition for either EG or the more serious disorder, HG. EG is usually defined as nausea, vomiting and/or the urge to vomit that occurs in the I trimester without any other cause.

According to the most recent American College of Obstetricians and Gynaecologists (ACOG, 2018) guidelines on nausea and vomiting in pregnancy, there is no single, universally accepted definition of HG, and the diagnosis is based on the exclusion of other possible causes [8]. The most commonly cited criteria for the diagnosis of HG include persistent vomiting not associated with other medical causes, acute fasting (usually significant ketonuria), electrolyte and acid-base disturbances, and weight loss >5% of the pregnant woman's original body weight [55].

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists' clinical practice guideline (2020) summarises all definitions of HG used in the literature, which were developed in accordance with the CoRe Outcomes in Women and Newborn Health Initiative (CROWN). The criteria most commonly cited as diagnostic of HG include: persistent vomiting with weight loss unrelated to other causes, together with an objective indicator of acute starvation, such as carbohydrate deficiency or deficit, electrolyte imbalance and/or acid-base imbalance [40, 43].

The criteria of the International Classification of Diseases (ICD-10) are similar, but indicate a possible duration of HG up to 22 weeks of pregnancy [65]. The extent of weight loss required to meet the criteria for HG is often defined as at least 5% of pre-pregnancy weight [59].

Ketonuria is often cited as a measure of dehydration or a sign of intoxication in HG, but a systematic review and meta-analysis found that ketonuria was not associated with either the diagnosis or severity of HG [52]. Most of these patients also have hyponatraemia, hypokalaemia, and low serum urea levels [67]. Ptyalism is also a typical symptom of HG. Symptoms of this disorder usually peak at 9 weeks of pregnancy and decrease until around 20 weeks of gestation [68].

Approximately 1% to 5% of patients with EG require hospitalisation. Women who had EG during their first pregnancy are at high risk of recurrence [4]. Although there may be a continuum between HG and EG, it is important to distinguish between these conditions, as treatment and potential complications differ significantly between women and fetuses [47]. The severity of HG is determined using information on metabolic abnormalities, clinical codes for severe HG, and inpatient treatment with a primary diagnosis requiring intravenous infusion and parenteral nutrition.

As noted in the previous meta-analysis by V. I. Medved et al. (2023), there are several scoring systems for quantifying nausea and vomiting, including the Motherisk Pregnancy-Unique Quantification of Emesis and Nausea (PUQE), which is recognised as simpler and more reliable [4]. The PUQE system determines the severity of nausea and vomiting based on three questions: duration of nausea, frequency of vomiting and vomiting urges within 24 hours. This scale has been found to correlate strongly with women's self-reported general physical and mental well-being ($p<0.001$), as well as with relevant practical measures of severity, such as the need for hospitalisation and emergency department care [43].

Pharmacological treatment of EG and HG should be used as part of a holistic therapy approach, including, whenever possible, non-pharmacological interventions and psychosocial support [2, 4]. Almost all pharmacological treatments are "off-label" and based on historical experience with limited high-quality evidence-based data described in small studies or systematic reviews or meta-analyses. In all cases, a rational assessment of maternal and fetal risk, including teratogenesis, should be based on the individual context of the pregnant woman.

Despite the fact that EG and HG are common problems in pregnant women, there is a lack of research focusing on therapeutic strategies, especially on optimal infusion therapy. The reason may be that the primary focus of the treatment strategy for HG is on antiemetics, while the use of infusion therapy is largely underestimated.

Recent pathophysiological studies on HG have improved awareness and appropriate antenatal care of pregnant women with a drug combination, which is critical for further efforts to address this problem and prevent polypharmacy. Therefore, the purpose of our analytical review is to study the available randomised controlled trials on drug therapy for HG with a focus on adequate infusion support to improve the quality of care for pregnant women, evaluating them based on objective measures of efficacy, safety for women and fetuses, and economic costs.

Data sources: Data on EG and HG were obtained using ICD 9/10 codes.

The databases MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Scopus scien-

tific citation, Conference Proceedings Index, NHS Economic Evaluation Database, Health Economic Evaluation Database, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects and publications in Ukrainian professional journals were searched using the following terms: pregnancy, pregnancy nausea and vomiting, excessive pregnancy vomiting, hyperemesis, antiemetic therapy during pregnancy, infusion therapy, and safety profile of medications prescribed during pregnancy in various combinations. The relevant articles were reviewed and additional sources were found in the references to these articles. The search was conducted from the beginning of 2013 to April 2023.

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

The choice of antiemetic should be individualised, based on the woman's symptoms, previous response to treatment and potential adverse events: if an antiemetic medication is ineffective at maximal dose, discontinue before commencing an alternative agent. If an antiemetic drug is partially effective, optimise dosage and timing, only add additional agents after maximal doses of the first agent have been trialled. If there is no drug allergy, prescribe each medication for 24 hours before advancing to the next treatment line [34].

Evidence from 35 randomised controlled trials (RCTs) at low risk of bias indicated that ginger, vitamin B6, antihistamines, metoclopramide (for mild symptoms), pyridoxine-doxylamine, and ondansetron (for moderate symptoms) were associated with improved EG symptoms compared with placebo. One RCT (n = 86) reported greater improvements in moderate symptoms following psychotherapy (change in Rhodes score (range: from 0 - no symptoms to 40 - worst possible symptoms) - 18.76 (standard deviation (SD) 5.48 to 7.06 (SD 5.79) for intervention vs 19.18 (SD 5.63) to 12.81 (SD 6.88) for comparison ($p< .001$). For moderate-severe symptoms, 1 RCT (n = 60) suggested that pyridoxine-doxylamine combination taken preemptively reduced risk of recurrence of moderate-severe symptoms compared with treatment once symptoms begin (15.4% vs 39.1%; $p < .04$).

One RCT (n = 83) found that ondansetron was associated with lower nausea scores on day 4 than metoclopramide (mean visual analogue scale (VAS) score, 4.1 (SD 2.9) for ondansetron vs 5.7 (SD 2.3) for metoclopramide ($p = .023$) but not episodes of emesis (5.0 (SD 3.1) vs 3.3 (SD 3), respectively ($p = .013$)). Although there was no difference in trend in nausea scores over the 14-day study period, trend in vomiting scores was better in the ondansetron group ($p = .042$). One RCT (n = 159) found no difference between metoclopramide and promethazine after 24 hours (episodes of vomiting, 1 (IQR 0-5) for metoclopramide vs 2 (IQR 0-3) for promethazine ($p = .81$), VAS (0-10 scale) for nausea, 2 (IQR 1-5) vs 2 (IQR 1-4), respectively ($p = .99$).

Three RCTs compared corticosteroids with placebo or promethazine or metoclopramide in women with severe symptoms. Improvements were seen in all corticosteroid groups, but only a significant difference between corticosteroids vs metoclopramide was reported (emesis reduction, 40.9% vs 16.5% at the 2d day; 71.6% vs 51.2% at the 3d day; 95.8% vs 76.6% at the 7th day ($n = 40$; $p < .001$). For other interventions, evidence was limited.

For mild symptoms of nausea and emesis of pregnancy, ginger, pyridoxine, antihistamines, and metoclopramide were associated with greater benefit than placebo. For moderate symptoms, pyridoxine-doxylamine, promethazine, and metoclopramide were associated with greater benefit than placebo. Ondansetron was associated with improvement for a range of symptom severity. Corticosteroids may be associated with benefit in severe cases. Overall the quality of evidence was low [48].

In another meta-analysis, seventy-three studies on the use of therapeutic strategies for EG and HG met the inclusion criteria: 33 and 11 studies had a low and high risk of bias respectively. The most common were steroid versus usual treatment and vitamin B6 versus placebo. There was evidence that ginger, antihistamines, metoclopramide (mild disease) and vitamin B6 (mild to severe disease) are better than placebo.

Diclectin® (Duchesnay Inc.) doxylamine succinate (10 mg) plus pyridoxine hydrochloride (10 mg) slow release tablet is more effective than placebo and ondansetron is more effective at reducing nausea than pyridoxine plus doxylamine. Diclectin before symptoms of EG begin for women at high risk of severe HG recurrence reduces risk of moderate/severe ET compared with taking Diclectin once symptoms begin.

Promethazine is as, and ondansetron, is more effective than metoclopramide for severe HG. Infusion therapy helps to correct dehydration and improve symptoms. Dextrose solution may be more effective at reducing nausea than normal saline. Transdermal clonidine patches may be effective for severe HG. Enteral tube feeding is effective but this extreme treatment method is suitable for very severe symptoms. Outpatient treatment for moderate/severe symptoms is feasible, acceptable and as effective as inpatient care. For all other interventions and comparisons, evidence is unclear.

The economic analysis was limited by lack of effectiveness data, but comparison of costs between treatments highlights the outcomes of different approaches. Thus, there was evidence of some improvement in symptoms for some treatments, but these data may not be transferable across disease severities. Methodologi-

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Table 1

Antiemetics that can be used parenterally [39]

Agent	Dose	Note
Metoclopramide	10 mg IV (0.5 mg/kg to a maximum of 30 mg/day), or 1.2-1.8 mg/hour infusion, or SC 20-40 mg/day	Slow IV infusion over 2-20 min Sedation
Cyclizine	50 mg slowly IV	Deep sedation
Droperidol	0.5-1 mg/h (25 mg/day)	Sedation
Promethazine	25 mg IM or IV (100 mg/day)	Sedation
Prochlorperazine	5 to 10 mg IV	Sedation
Ondansetron	4-16 mg IV Subcutaneous infusion (pump) 16-28 mg/day	Avoid in women with Q-T prolongation
Methylprednisolone	16 mg over 48-72 hours	
Hydrocortisone	100 mg/day IV	

cally sound and larger trials of the main therapies are needed [7, 53].

According to the recommendations of many national guidelines [8, 34, 43, 50, 59], depending on the severity of EG, the first step is usually to start with the oral treatment, but in the case of HG, intravenous or subcutaneous treatment is recommended (Tab. 1).

For some agents, such as ondansetron, oral forms are available, but they are not absorbed sublingually and must be swallowed as tablets or syrup. The outpatient continuous use of subcutaneous antiemetics has been described in a number of observational studies [39].

Subcutaneous ondansetron is more effective than subcutaneous metoclopramide, although both agents significantly reduce the risk of readmission. However, almost half of the women still required intravenous hydration during the treatment period, and patients remained on therapy for an average of 22.3±2.2 days [39]. To date, subcutaneous microinfusion pumps of these antiemetics are not cost-effective compared to conventional treatment alternatives, including periodic hospitalisation [58].

According to the American College of Obstetrics and Gynaecology (ACOG) Nausea and Vomiting in Pregnancy Guidelines (2018), first-line pharmacological therapy should include a combination of vitamin B6 (pyridoxine) and doxylamine. The ACOG endorses three dosing regimens: 10 to 25 mg of pyridoxine orally with 12.5 mg of doxylamine three or four times daily, 10 mg of pyridoxine and 10 mg of doxylamine up to 4 times daily, or 20 mg of pyridoxine and 20 mg of doxylamine up to 2 times daily [8].

Second-line medications include antihistamines and dopamine antagonists, such as dimenhydrinate 25-50 mg every 4-6 hours orally, diphenhydramine 25-50 mg every 4-6 hours orally, prochlorperazine 25 mg every 12 hours rectally, or promethazine 12.525 mg every 4-6 hours orally or rectally.

If a patient still has significant symptoms without signs of dehydration, metoclopramide or ondansetron can be administered orally. In the case of dehydration, intravenous infusion of saline solutions should be used in addition to intravenous metoclopramide, ondansetron or promethazine.

Rehydration, together with electrolyte replacement, is very important in the treatment of HG. Suitable solutions are saline or Hartmann's solution. Potassium chloride can be added if necessary. Electrolytes should also be added as needed. In severe refractory cases of HG, intravenous or intramuscular administration of 25-50 mg of chlorpromazine or 16 mg of methylprednisolone every 8 h orally or intravenously is preferred [48].

The promising areas to be investigated in the near future: evaluation of the effect of ondansetron and mirtazapine in the treatment of HG: a double-blind, randomised, placebo-controlled, multicentre trial (ongoing until 2023); chewing gum containing vitamin C for the treatment of EG: a randomised controlled trial [36].

Twenty-five trials (2052 women) met the inclusion criteria regarding the treatment of EG and HG (2018). There was insufficient evidence to identify clear differences between acupuncture and metoclopramide in a study regarding reduction/cessation in nausea or vomiting (risk ratio (RR) 1.40, 95% CI 0.79-2.49 and RR 1.51, 95% CI 0.92-2.48, respectively). Midwife-led outpatient care was associated with fewer hours of hospital admission than routine inpatient admission (mean difference (MD) - 33.20, 95% CI -46.91 to -19.49) with no difference in pregnancy-unique quantification of emesis and nausea (PUQE) score, decision to terminate the pregnancy, miscarriage, small-for-gestational age infants, or time off work when compared with routine care.

Women taking vitamin B6 had a slightly longer hospital stay compared with placebo (MD 0.80 day, 95% CI 0.08-1.52). There was insufficient evidence to demonstrate a difference in other outcomes including mean number of episodes of emesis (MD 0.50, 95%

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CI -0.40-1.40) or side effects. A comparison between metoclopramide and ondansetron identified no clear difference in the severity of nausea or vomiting (MD 1.70, 95% CI -0.15-3.55, and MD -0.10, 95% CI -1.63-1.43; one study, 83 women, respectively). However, more women taking metoclopramide complained of drowsiness and dry mouth (RR 2.40, 95% CI 1.23-4.69, and RR 2.38, 95% CI 1.10-5.11, respectively). There were no clear differences between groups for other side effects.

In a single study with 146 participants comparing metoclopramide with promethazine, more women taking promethazine reported drowsiness, dizziness, and dystonia (risk ratio (RR) 0.70, 95% CI 0.56-0.87, RR 0.48, 95% CI 0.34-0.69, and RR 0.31, 95% CI 0.11-0.90, respectively). There were no clear differences between groups for other important outcomes including quality of life and other side effects.

In a single trial with 30 women, those receiving ondansetron had no difference in duration of hospital admission compared to those receiving promethazine (mean difference (MD) 0.00, 95% CI -1.39-1.39), although there was increased sedation with promethazine (RR 0.06, 95% CI 0.00-0.94).

Regarding corticosteroids, in a study with 110 participants there was no difference in days of hospital admission compared to placebo (MD -0.30, 95% CI -0.70-0.10), but there was a decreased readmission rate (RR 0.69, 95% CI 0.50-0.94; 4 studies, 269 women).

For hydrocortisone compared with metoclopramide, no data were available for primary outcomes and there was no difference in the readmission rate (RR 0.08, 95% CI 0.00-1.28; one study, 40 women). In a study with 80 women, compared to promethazine, those receiving prednisolone had increased nausea at 48 h (RR 2.00, 95% CI 1.08-3.72), but not at 17 days (RR 0.81, 95% CI 0.58-1.15). There was no clear difference in the number of episodes of emesis or subjective improvement in nausea/vomiting. While there were a wide range of interventions studied, both pharmaceutical and otherwise, there was a limited number of placebo controlled trials.

In comparing the efficacy of the commonly used antiemetics, metoclopramide, ondansetron, and promethazine, the results of this review do not support the clear superiority of one over the other in symptomatic relief.

Other factors such as side effect profile medication safety and healthcare costs should also be considered when selecting an intervention [14]. Modern, personalised therapeutic strategies for EG and HG can improve pregnancy outcomes and reduce unnecessary treatment through the use of evidence-based pharmacological interventions that are efficacious, safe and cost-effective [50]. Therefore, below we will try to summarise the results of good pharmacological practice in the treatment of EG and HG.

Ondansetron is a 5-HT3 receptor antagonist that has been approved for the prevention of nausea and vomiting associated with cancer chemotherapy, surgery and pregnancy [11]. Previous studies have indicated that it is the most common antiemetic agent used to treat EG and HG in the United States [57]. A systematic review and meta-analysis regarding the risk of major congenital malformations identified no significant increased risk for associated major or individual subgroups of malformations, especially for heart defects and orofacial clefts [37].

A clinical trial in Western Australia (251 pregnant women) also did not detect any adverse outcomes from the use of ondansetron in pregnancy [18]. However, rare adverse events include Q-T interval prolongation and serotonin syndrome (which can include agitation, fever, and increased reflexes) [51].

In addition, S. F. Fejzo et al [2016] compared the outcomes of 1841 pregnancies with HG with and without ondansetron and found that women who took ondansetron reported significantly less terminations due to HG and lower rates of miscarriages in the first 12 weeks of gestation. Women who used ondansetron were more likely to report completing their pregnancy to 37 weeks' gestation [23].

In 2015, Z. A. Flake et al. found that ondansetron reduces nausea and vomiting in children with acute gastroenteritis and in women with EG and HG by blocking dopamine in the intestines and chemoreceptor trigger zone [26]. Another RCT of 36 pregnant women showed ondansetron to be superior to the combination of pyridoxine and doxylamine in the treatment of nausea and emesis in pregnancy [54]. Also, based on the study by M. Kashifard et al., ondansetron group had significantly lower vomiting scores than metoclopramide group (83 pregnant women, mean gestational age 8.7 weeks) [38]. Moreover, it was demonstrated that ondansetron and metoclopramide demonstrated similar antiemetic and antinauseant effects in HG. However, the overall profile, particularly regarding adverse effects, was better with ondansetron [6].

The safety of ondansetron during pregnancy was reported in a Danish study of 1970 infants, who showed no increased risk of fetal malformations or adverse pregnancy outcomes [21]. The study also demonstrated that ondansetron does not appear to be associated with an increased risk for major malformations above baseline, indicating its safety in pregnancy [21].

However, some studies have linked ondansetron to certain congenital malformations. A Swedish cohort of 1,349 pregnant women showed an increased risk of cardiac septal defects [19], and a US cohort study also reported an increased risk of orofacial clefts [10].

An updated recent meta-analysis of 12 comparative studies (2022) revealed that exposure to ondansetron during the I trimester correlated with higher signifi-

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cant risks for ventricular septal defects (n=6 studies, odds ratio=1.11) and orofacial clefts (n=5 studies, odds ratio=1.48). However, no substantial connection was identified for various cardiac-related defects and craniofacial anomalies [9].

In addition, C. R. Dormuth et al (2021) conducted a large multicentre, cohort study involving 456,963 pregnancies, comparing various pregnancy outcomes among women treated with ondansetron or alternative antiemetics. The study demonstrated no association between ondansetron exposure during pregnancy and increased risk of fetal death, spontaneous abortion, stillbirth, or major congenital malformations compared with exposure to other antiemetic drugs [20].

The results obtained suggested that ondansetron is generally safe and its use is strongly recommended during and after the I trimester. The risk of orofacial clefts due to ondansetron exposure remains a subject of controversy in large cohort studies [20]. At the same time, we should mention that in 2018, a US court found a causal link between the use of ondansetron in the I trimester and the occurrence of congenital heart defects in the fetus. After that, the US Food and Drug Administration (FDA) ordered pharmaceutical manufacturers of ondansetron-containing products to include this information in the labelling of these products [8].

The future studies should examine whether this potential teratogenic risk is greater than the risk of adverse outcomes of untreated HG.

Pyridoxine, a vitamin B6 vitamer, is effective in relieving the severity of nausea in early pregnancy [64]. Z. A. Flake et al [2015] found that for treatment of mild pregnancy-induced nausea, pyridoxine with or without doxylamine is recommended [26]. Combination therapy with pyridoxine and metoclopramide appears to be superior to either monotherapy in the treatment of EG [16].

Another placebo-controlled study of 92 women, however, showed that the use of oral pyridoxine with metoclopramide during hospitalisation and for 2 weeks after discharge from hospital for the treatment of HG did not reduce the incidence of vomiting or nausea [61]. A cohort study also demonstrated that metoclopramide did not increase the risk of fetal malformations [56].

Promethazine is a predominantly antihistamine agent and also acts as a weak dopamine antagonist. It is an efficacious treatment for EG during pregnancy, but has significant adverse effects for the mother, including dystonia, sedation, and lowered seizure threshold [15]. Droperidol in combination with diphenhydramine has also been found to reduce the number of hospital stay days for women with HG; no correlation with fetal malformations was found, although there was an association with Q-T prolongation in some pregnant women [35].

Another study demonstrated that promethazine and metoclopramide have similar therapeutic effects in patients who are hospitalised for HG, but metoclopramide had less adverse effects [61]. In a study of 140 pregnant women, dimenhydrinate was more effective than vitamin B6 in the treatment of nausea and vomiting in early pregnancy [13].

Retrospective chart review of 1,064 women hospitalised for HG with metabolic disturbances between 2002 and 2019 showed that the use of meclizine, prochlorperazine, and ondansetron increased during this time. This led to a yearly increase in the percentage of women using any antiemetic of 1.5% (95%CI 0.6; 2.4) at pre-hospital stage, 0.6% (95%CI 0.2; 1.1) during hospitalisation, and 2.6% (95%CI 1.3; 3.8) at discharge. Overall, only 50% of the women received antiemetics pre-hospital.

Following the EMA warning (limiting metoclopramide treatment to a maximum of 5 days), prehospital use of metoclopramide dropped by 30% (95%CI 25; 36), while use of any antiemetic drug pre-hospital dropped by 20% (95%CI 5.7; 34). In timely association, the authors observed a decrease in gestational age (-3.8 days, 95%CI 0.6; 7.1) at first admission, as well as indication of increased rate of termination of pregnancy with an absolute increase of 4.8% (95%CI 0.9; 8.7) in 2014 [22].

A further 2021 clinical trial found that gabapentin was more effective than standard-of-care therapy for reducing EG and increasing oral nutrition and global satisfaction in outpatients with HG [30]. The addition of parenteral and oral corticosteroids to the treatment of women with HG did not reduce the need for rehospitalisation later in pregnancy compared to placebo [66]. Besides, glucocorticoids have been associated with an increased risk of orofacial clefts when used in the early I trimester [17].

For hydrocortisone compared with metoclopramide, no data were available for primary outcomes and there was no difference in the readmission rate (RR 0.08, 95% CI 0.00-1.28; one study, 40 women). In a study with 80 women, compared to promethazine, those receiving prednisolone had increased nausea at 48 h (RR 2.00, 95% CI 1.08-3.72; low quality evidence), but not at 17 days (RR 0.81, 95% CI 0.58-1.15; very low quality evidence). There was no clear difference in the number of episodes of emesis or subjective improvement in nausea/vomiting [14].

Other therapeutic options for refractory HG include transdermal clonidine to reduce symptoms in women intolerant of oral treatment. A randomised, placebo-controlled clinical trial of 13 patients using clonidine reported a significant reduction of HG symptoms and a reduction in the need for parenteral nutrition [45]. A study of 70 patients with HG showed a reduction in the frequency of rehospitalisation with diazepam compared with mono-infusion therapy [62].

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Table 2

Agents to treat GER during pregnancy [12]

Agent	Dose	Note
First line - Antacids		
Magnesium-, calcium- or aluminium-containing antacids	As needed (for mild symptoms)	No increase in the incidence of congenital malformations Constipation or diarrhoea at high doses
Second line - H2 histamine receptor blockers		
Famotidine	20 mg 1-2 times daily	No increase in the incidence of congenital malformations
Nizatidine	150 mg 1-2 times daily	
Third line - Proton pump inhibitors		
Omeprazole	20 mg 1-2 times daily 40 mg IV once daily	No increase in the incidence of birth defects Well tolerated Switch from intravenous to oral treatment as soon as possible
Lansoprazole	30 mg 1-2 times daily	
Rabeprazole	20 mg 1-2 times daily	
Esomeprazole	20 mg 1-2 times daily 20 mg IV 1-2 times daily	
Pantoprazole	40 mg 1-2 times daily 40 mg IV 1-2 times daily	

Agents used to treat EG or HG, such as ondansetron, can cause significant and symptomatic constipation in pregnant women. Increasing dietary fibre and fluid intake is the preferred treatment for constipation during pregnancy, although this may be challenging for women with dietary restrictions due to EG.

In a systematic review of treatments for constipation in pregnancy, stimulant laxatives appear to be more effective in improvement of constipation, but are accompanied by an increase in diarrhoea and abdominal discomfort, additional use of fibre supplementation may increase frequency of stools [60]. Non-absorbable stool softeners, such as docusate sodium, can be an effective laxative.

In refractory cases, the use of magnesium salts or lactulose is considered acceptable for use during pregnancy. Castor oil may stimulate uterine contractions, and excessive use of mineral oil may interfere with the absorption of fat-soluble vitamins, so these agents are generally avoided.

Stimulant laxatives, such as senna or bisacodyl, are effective but associated with abdominal discomfort and should be used with caution during pregnancy, although they do not increase the incidence of congenital malformations [44]. Overall, short-term use of stimulant laxatives is considered safe during pregnancy. Osmotic laxatives, such as lactulose, sorbitol or macrogol, may be required, although the large volume of fluid required for oral administration may be poorly tolerated.

As in general medical practice, prolonged use of laxatives in obstetrics should be avoided.

Fibre-containing bulking agents are probably the safest laxatives during pregnancy because they are not absorbed systemically. These agents take a few days to show their effects, so they are not suitable for relieving acute symptoms. They are also contraindicated in case of faecal retention. The adverse events associated with bulking agents include excessive gas, cramping, and bloating. Rectal treatment may also be required, including enemas with bisacodyl, sodium phosphate and citrate/lauryl sulfoacetate/sorbitol or glycerol suppositories [33].

Many women with vomiting during pregnancy also experience symptoms of gastroesophageal reflux (GER), and the presence of such symptoms is associated with HG [28]. Treatment of GER along with antiemetic therapy was associated with a decrease in PUQE-24 scores (from 9.6±3.0 to 6.5±2.5; $p<0.0001$) and an improvement in quality of life (from 4.0±2.0 to 6.8±1.6; $p<0.0001$) (Tab. 2).

The mechanism of this association is primarily related to gastroesophageal motility. Gastric neuromuscular abnormalities associated with symptomatic nausea during pregnancy include gastric dysrhythmias, both brady- and tachy- [44]. In HG, the gastric myoelectric pattern is flat or arrhythmic. The mechanisms underlying this gastric arrhythmia are not well understood.

Concerns have been raised about an increased risk of childhood asthma in the children of women treated with acid suppressants, but no studies have considered the full panel of known disorders and the true risk has not been determined [43].

As a rule, the severity of EG can be assessed using the PUQE questionnaire during pregnancy. A score between 3–6 points was defined as mild EG, 7–12 points as moderate EG and scores ≥13 points was classified as severe EG. Severe (PUQE score >13) or prolonged (>14 days) moderate EG requires an assessment of the patient's general health, including weight loss, ketonuria, and dehydration, i.e. signs of HG, and the need for

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Table 3

Infusion therapy for excessive vomiting in pregnancy

Agent	Amount/rate	Note
Sodium lactate (Hartmann's solution) [44].	1-2 l/day: 1 l over 2 h, followed by 1 l over 4 h	An isotonic solution can be used intravenously for slow hydration (over 6-8 h). Consider adding 20 mmol potassium chloride
Sodium chloride 0.9%	1 l of fluid should be infused over 4 h, then 500 ml every 4-6 hours	Avoid rapid administration (may lead to central pontine myelinolysis) [43]. In case of hypokalaemia (K+ <3.5 mmol/l), 1000 ml of 0.9% sodium chloride with 20 mmol potassium is administered over 4 h [31].
A solution of 4% dextrose and 0.18% sodium chloride or 5% dextrose [43].	1 l / 1 l/h	Consider as an option if oral administration is not possible, in case of fasting or uncontrollable nausea, and only after thiamine deficiency has been corrected and hyponatraemia ruled out
Potassium chloride [43]	30-40 mmol/l. Maximum infusion rate: 10 mmol over 1 hour	Use with caution. The most optimal is the use of a mixture of 30 mmol potassium chloride and 1 l of 0.9% sodium chloride. Use only access to a large peripheral or central vein. Injection of potassium solution through small veins causes pain and irritation
Magnesium sulfate [43]	10-20 mmol/day over 20-40 min	Dilute 100 ml with 0.9% sodium chloride solution. Use only access to a large peripheral or central vein
Xylat [1,49]	6-8 ml/kg body weight	Duration of treatment: 3-5 days

hospitalisation should be considered. Intravenous solutions and/or parenteral nutrition or tube feeding can be used in outpatient settings [46].

When prescribing infusion therapy, physicians must take into account the osmolarity of infusion solutions and compare it with the osmolarity of blood plasma, which is normally 290 mOsm/l and does not change during pregnancy. Infusion solutions can be divided into hypoosmolar (hypotonic), hyperosmolar, and isotonic (isoosmolar) according to their osmolarity. Hyperosmolar solutions should be administered for the transfer of fluid from the intercellular space to the vascular bed; for the reverse movement of fluid outside the bloodstream (which is much less common in clinical practice), hypoosmolar solutions should be used.

Osmolarity of some infusion solutions:

1. Crystalloids:

- Sodium chloride 0.9% - 308 mOsm/l;
- Ringer's solution - 320 mOsm/l;
- Ringer's lactate solution - 270 mOsm/l;
- 4-5% glucose - 278 mOsm/l;
- 10% glucose - 556 mOsm/l.

2. Polyhydric alcohols:

- Rheosorbilact - 900 mOsm/l;
- Sorbilact - 1670 mOsm/l;
- Xylat - 610 mOsm/l [49].

Intravenous rehydration is usually recommended for patients with HG and severe dehydration or ketonuria. Rapid rehydration of women usually alleviates many of the HG symptoms. In a systematic review (2016), the researchers found that 4-5% glucose saline may be associated with better improvement than normal saline in moderate to severe cases (n=222) [48]; however, there is a risk of developing Wernicke encephalopathy.

Intravenous fluid administration helps to correct dehydration and electrolyte disturbances and has been shown to reduce vomiting in pregnant women, even without antiemetics [44]. When prescribing intravenous fluid therapy, the degree of dehydration and any electrolyte disturbances should be taken into account (Tab. 3).

Severe hyponatraemia must not be corrected faster than 10 mmol/l in 24 hours to prevent central pontine myelinolysis. Current data do not indicate a superiority of dextrose-based fluids over saline.

Caution should be exercised when using any dextrose-based solution, as there is a risk of developing Wernicke encephalopathy (ophthalmoparesis with nystagmus, ataxia and confusion may occur in thiamine-deficient women). If dextrose solutions are used, 200-300 mg of thiamine should be added to the infusion [25, 44].

The Greater Glasgow & Clyde Obstetric Guidelines (2020) recommend the following infusion therapy regimen:

- 1000 ml of Hartmann's or Sodium Chloride 0.9% over one hour
- 500 ml of Hartmann's or Sodium Chloride 0.9% with 20 mmol KCL over 2 hours
- 500 ml of Hartmann's or Sodium Chloride 0.9% with 20 mmol KCL four hourly [31, 32].

In Ukraine, the most commonly used products to treat hypovolaemia, dehydration and detoxification, as well as to improve haemodynamics and rheological properties of blood in pregnancy complications are the polyhydric alcohols Rheosorbilact and Xylat.

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Rheosorbilact is a multicomponent hyperosmolar crystalloid containing sorbitol polyhydric alcohol and electrolytes in a concentration that restores electrolyte balance, provides a pronounced detoxification effect due to its high water index and promotes the elimination of toxins through diuretic action, improves microcirculation and is used for complex rehydration. The dosage of Rheosorbilact is 7 ml/kg per day.

Main therapeutic effects of Rheosorbilact:

- Sorbitol – improvement of capillary blood flow, detoxification, improvement of blood rheological properties;
- Sodium lactate - correction of metabolic acidosis, normalisation of metabolic processes in tissues;
- Balanced electrolyte complex – correction of blood water and electrolyte composition.

Xylat (xylitol + sodium acetate) is a multicomponent hyperosmolar solution with anti-ketogenic, nitrogen-saving and lipotropic effects. At the same time, xylitol contained in the solution does not affect blood glucose level and does not promote endogenous insulin secretion, and sodium acetate provides acidosis correction without sharp pH fluctuations [49].

Given that the consequence of HG is ketoacidosis with hepatic lipase activation, triglyceride breakdown, and the formation of excess acetylcoenzyme A, which is not fully used in the Krebs cycle and is a source of ketone bodies that exist in the human body in the form of three compounds: acetoacetic β-oxybutyric acids and acetone, the infusion of the multinuclear alcohol xylitol is considered to be quite justified, since energy production in cells, including the liver, occurs without the use of insulin, which is extremely important [49].

Mechanisms of action of xylitol:

- reduction of ketogenic intoxication and promotion of glycerophosphate formation through the pentose phosphate cycle, thus reducing the amount of fatty acids that can be oxidised to acetyl coenzyme A;
- through activation of glycolysis, it increases the formation of pyruvic acid, which causes oxidation of acetylcoenzyme A in the Krebs cycle;
- acceleration of glycogen formation in the liver, reduction of fat mobilisation in the periphery (lipolysis);
- increasing of ATP content in the liver;
- promotion of endogenous insulin synthesis, improvement of carbohydrate metabolism;
- significantly reduction of lactate concentration and gluconeogenesis rate compared to isocaloric glucose.

In view of the electrolyte content and osmolarity of Xylitol, it is quite reasonable to use it to restore fluid volume in the vascular bed [49].

According to the results of a prospective clinical study by Kim Eun-Din (2012), pregnant women using Xylat have faster dehydration, significantly improved haemodynamic profile within 2 hours after the start of infusion therapy. When Xylat was used in pregnant women, biochemistry parameters normalised faster (blood β-hydroxybutyrate concentration normalised and urinary acetone levels decreased, serum urea, creatinine and glucose levels decreased, electrolyte composition stabilised) [1].

In the case of severe dehydration, before using hyperosmolar solutions, an infusion of simple crystalloids (0.9% sodium chloride solution) should be performed to normalise the tissue water balance and reduce the tissue toxin concentration. The next step is to create conditions for the transfer of dissolved toxins from the tissues to the vascular bed. This is achieved through the use of hyperosmolar balanced infusion solutions with a high volumetric index, for example, solutions based on the polyhydric alcohols sorbitol and xylitol [3, 49].

If antiemetics and infusion therapy are not adequate to reduce nausea and/or vomiting, ketonuria persists, and the patient is unable to improve food intake, additional parenteral therapy should be considered; however, parenteral nutrition in early pregnancy HG has rarely been reported. Enteral feeding can be performed through a jejunal tube placed by gastroscopy. N. Vaisman et al. (2004) found that nasojejunal enteral feeding may affect the movement of the digestive tract, thus suppressing vomiting during pregnancy. A clear reduction in the extent of vomiting was already apparent within the first 48 h after tube insertion, but vomiting ceased completely after a mean of 5+/-4 days (range 1-13 days). The above suggests that nasojejunal enteral feeding can significantly reduce vomiting due to the effect on the movement of the digestive tract [63].

A study by J. J. Hsu et al. (1996) reported that the placement of a Dobhof tube improved nausea and vomiting symptoms within 24 hours, and that the symptoms of HG continued to improve with enteral feeding. The average duration of hospitalisation after the start of feeding was 4.6 days, with the longest being 8 days [69].

However, parenteral nutrition is rarely used in early pregnancy for HG, but some studies have shown that parenteral nutrition through PEG-jejunostomy (PEG-J) tubes during pregnancy can also reduce residual gastric volume, thus reducing the frequency of vomiting [27].

R. M. Gulley et al [1993] reported that enteral feeding through an iso-osmolar nasogastric tube increased gastric motility, reducing the symptoms of HG. In 30 patients with HG, it was demonstrated that this approach was superior to intravenous therapy and antiemetics in controlling nausea [29].

This treatment has potential complications, such as aspiration, infection, venous thrombosis, intrahepatic

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cholestasis and fatty infiltration of the placenta. To minimise the possibility of aspiration, the tube should be placed behind the pylorus. Even though it is expensive, this method is much cheaper than full parenteral nutrition. This type of feeding is most beneficial for pregnant women who have nausea and vomiting associated with food intake [69].

In 2018, the first genome-wide association study (GWAS) of EG and HG provided new information about their aetiology, demonstrating that the placenta and the appetite gene GDF15 are genetic risk factors [24]. Therefore, efforts should be focused on whether GDF15-encoded proteins can be used to diagnose, predict and treat EG and HG. Agents targeting the GDF15-GFRAL pathway have also been developed to treat cancer-related cachexia, which correlates with high GDF15 levels [42]. Hence, the development of agents targeting the GDF15-GFRAL pathway, if proven safe during pregnancy, could help treat women with EG, and especially those with HG.

CONCLUSIONS

The choice of antiemetics should be considered as a "step-up" therapy that should be individualised based on the woman's symptoms, previous response to treatment and possible side effects.

Acute treatment of EG/HG can be focused on improving dehydration and/or electrolyte disturbances, controlling nausea and vomiting to ensure optimal enteral nutrition.

Women presenting to the emergency department require infusion therapy based on the severity of their EG/HG.

Including xylitol, a multinuclear alcohol, in the treatment regimen is an optimal addition to conventional treatment regimens for HG, especially for recurrent HG. Xylitol reduces ketogenic intoxication and ketone body synthesis by accelerating the oxidation of acetyl-CoA in the Krebs cycle, accelerates the excretion of ketone bodies from the body and corrects metabolic acidosis, and a balanced electrolyte composition restores their balance.

Additional acid-suppressive therapy will reduce nausea and vomiting even in the absence of typical reflux symptoms.

Both the underuse of safe treatments and the prolonged use of medications that have proven ineffective or caused unacceptable adverse events should be avoided.

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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