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Nausea and Vomiting of Pregnancy, Hyperemesis gravidarum

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Approved by the Academy for Feto-Maternal Medicine AFMM

	Evidence-levels
Definitions and Epidemiology	
Nausea with or without vomiting in early pregnancy (NVP) is very common (50-80%). Severe vomiting termed hyperemesis gravidarum (HG) occurs in 0.3-3% (1). The most commonly cited criteria to define HG include persisting vomiting, acute dehydration and starvation (ketonuria) and weight loss >5%. It is a clinical diagnosis of exclusion based on a typical presentation, in the absence of other causes that could explain the symptoms (2).	Ia IIa
Symptoms typically appear before 9 weeks of gestation and resolve by 16 weeks of gestation, rarely they persist throughout pregnancy (10-20%) (3). The disorder is likely to reoccur in subsequent pregnancies (24-80%, OR=26.4, CI 95%)(4).	IIa IIa
Etiology and Risk Factors	
Precise etiology remains unknown, various theories, however, have been proposed: hormonal factors (↑βHCG, ↑estradiol), mechanical factors (intestinal distention, reflux), psychologic predisposition, evolutionary adaptation (avoidance of potentially toxic food) and genetic risk factors (↑placental gene GDF15, IGFBP7 hormone, RyR2 gen) (5-8). The cause is most likely multifactorial. Further risk factors include high placental mass (i.e. multiple pregnancy or molar gestation), personal and family history (3).	IIa/III IIa
Differential diagnosis • *Gastrointestinal conditions*: gastroenteritis, gastroparesis, gastritis/peptic ulcer disease (H. pylori), biliary tract disease, hepatitis, intestinal obstruction, pancreatitis, appendicitis, internal hernia after gastric bypass surgery (9) • *Conditions of the genitourinary tract:* pyelonephritis, uremia, ovarian torsion, kidney stones, degeneration uterine leiomyoma • *Endocrine, metabolic conditions, neurologic disorders:* diabetic ketoacidosis, porphyria, Addison's disease, hyperthyroidism, hyperparathyroidism, hypercalcemia, migraine, raised intracranial pressure, labyrinthitis • *Miscellaneous conditions:* drug toxicity or intolerance, psychological conditions • *Pregnancy-related conditions:* preeclampsia after 20 weeks of gestation, HELLP-syndrome, acute fatty liver of pregnancy	
Complications *Maternal* complications such as suicidal ideation (32%), weight loss >15% and fulfilled criteria of post-traumatic stress disorder associated depression (18%) are frequent. Although rare, severe *maternal* morbidity/mortality has been reported too: Nutritional deficiency, such as Wernicke encephalopathy (caused by vitamin B complex deficiency), electrolyte disturbances, thromboembolic events, thyrotoxicosis. Furthermore, detached retinas, pneumothorax, rib fractures, gall bladder dysfunction, acute tubular necrosis, splenic avulsion, hepatic insufficiency, hematemesis (bleeding originating from small ruptured esophageal vessels, Mallory-Weiss syndrome), and an increase of hospital admissions have been associated to HG (10-13).	III/IIa
A lower rate of miscarriage among women with HG when compared with controls has been documented (14).	Ib
For *fetal* complications, a systematic review of women with HG showed a slightly but significantly higher incidence of intrauterine growth restriction / low birth weight and prematurity (15). These observations seem to be more common if HG persists throughout pregnancy requiring multiple hospitalizations with no 'catch up' weight gain. If maternal weight loss exceeds 15% smaller head circumference, significantly reduced total cortical volume and increased risk of neurodevelopmental delay and autism have been described (16, 17).	IIa IIb

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Comorbidities

The following comorbidities are associated with higher risk of HG: Parathyroid dysfunction aOR 3.83 (95%; CI 2.28-6.44), hypercholesterolemia aOR 2.54 (95%, CI; 1.82-3.44), type 1 Diabetes aOR 1.95 (95%; CI 1.82-2.09) and thyroid dysfunction aOR 1.85 (95%, CI; 1.74-1.96) (18). IIb

Evaluation and assessment of severity

All women should be asked about NVP at each medical visit, and if present, severity should be assessed with a validated scale, weigh measurement and hydration status. Medical history must focus on exclusion of differential diagnosis and assessment of severity of HG. Using a score to identify severity of HG is recommended. The Pregnancy-Unique Quantification of Emesis (PUQE-24) Scale (19) IV
has now been implemented in most guidelines (2, 20). A recent publication suggest the alternative III
HELP-score to have better sensitivity in identifying patients with severe HG symptoms requiring interventions (Free iOS HG Care App ©The HER Foundation) (21). IIa

PUQE score

How often have you felt sick in the past 24 hours?	Have you vomited in the last 24 hours)	How often have you choked in the past 24 hours?
❒ Not at all (1)	❒ No (1)	❒ Never (1)
❒ 1h or less (2)	❒ 1 - 2 times (2)	❒ 1 – 2 times (2)
❒ 2h – 3h (3)	❒ 3 – 4 times (3)	❒ 3 – 4 times (3)
❒ 4h – 6h (4)	❒ 5 – 6 times (4)	❒ 5 – 6 times (4)
❒ > 6h (5)	❒ 7 or more times (5)	❒ 7 or more times (5)

Mild: <6 points, moderate: 7 - 12 points, severe (HG): 13 - 15 points

Outpatient treatment: PUQE score from 3 to 12
Inpatient treatment recommended: PUQE score ≥ 13

In addition to the regular pregnancy control (vital parameters, weight), clinical evaluation comprises Ultrasound examination (exclusion of multiple pregnancies or molar gestation), urine status (ketonuria and exclusion of a urinary infection) and blood analysis (blood count, electrolytes, renal and hepatic function, thyroid function). In severe cases, further blood analysis (e.g. blood gas analysis, vitamin B1) and eventually other examinations to exclude an underlying pathologic condition should be considered.

Treatment

Management and treatment of NVP must focus on reducing symptoms, improving quality of life, preventing serious complications and minimizing fetal effects of maternal pharmacologic treatment.
An early and stepwise approach is recommended (22) (see algorithm). Ib

Dietary and lifestyle recommendations

- Avoid an empty stomach at all times, with small and frequent meals every 1-2 hours (2) IV
- Prevent a full stomach (i.e. not mixing solid with liquid, avoiding large meals) (23) III
- Eat dry food, high-protein snacks, and crackers in the morning before arising (24, 25) IIa/III
- Avoid strong tasting and spicy food, eliminate supplemental iron (24) IIa

Alternative Treatments

Ginger

Ginger (as rhizoma zingiberis) in pregnancy for the use of NVP is described in several RCTs (1): There was no evidence for an increased risk of teratogenicity and no evidence for spontaneous abortion or difference in pregnancy outcome between the treatment groups. Ginger shows anti-inflammatory properties lowering thromboxane B(2) and PG E(2) levels in animals (26), as a result, it should not be used by anticoagulated patients. Ginger has shown a beneficial effect in reducing nausea symptoms, but not in reducing vomiting (1, 27). Ia Ia

Acupuncture and acupressure at P6 or Neiguan point (located three fingerbreadths below the wrist on the inside of the wrist between the two tendons) have not been proven to significantly reduce nausea and vomiting (27, 28). Nevertheless, given the absence of harm and the strong placebo effect, some patients may benefit from a trial of acupressure bands. IIa/Ia

Pharmacological treatment

Pyridoxine (vitamin B6)

The effectiveness of oral pyridoxine alone in the treatment of morning sickness (but not vomiting!) has been shown in placebo-controlled studies (1). Orally in combination with an antihistaminic drug (see below) for patients with NVP and intravenously combined with other vitamins for hospitalised women with severe HG. As a water-soluble vitamin B6 it is toxicologically safe.	Ia
Antihistamines (H1-antagonists) H1-antagonists are effective for treatment of varying degrees of NVP, but the studies are heterogenous regarding the substance and combination with pyridoxine, e.g. (29).	
Meclozine (synonym meclizine): Considered safe during pregnancy: no signs of any significant teratogenicity has been shown (30). Meclozine is only available on the market in combination with pyridoxine and caffeine, which compensates the sedative effect of the antihistaminic because of its central and possibly also circulatory stimulating effect. An association of caffeine intake and increased risk of miscarriage, stillbirth, low body weight (LBW and SGA) and acute lymphoblastic leukemia in childhood with increasing doses of caffeine has been shown (31). The dosage of caffeine in a pill is 25mg, in a suppository is 20 mg. The maximum doses are 4 pills (100 mg) or 2 suppositories (40 mg) per day, which correspond to a maximum of 1 coffee (100 mg) per day. It is therefore recommendable to advise pregnant women to stop other caffeine consumption ("stop coffee and other beverages containing caffeine").	IIb
Doxylamine: Has recently been approved by Swissmedic as drug against NVP in combination with pyridoxine. Its efficacy has been widely studied in observational studies with no teratogenic effect (29, 32, 33). A recent randomized double-blind placebo-controlled study in 256 patients with NVP proved the efficacy of the drug, while side effects were not different from placebo, probably due to small sample size (34). In a recent study, first-trimester doxylamine-pyridoxine and metoclopramide exposure was associated with a significantly increased risk of overall and specific major congenital malformations (MCM), such as spina bifida (35). Note: –Doxylamine is effective to improve sleep because of its sedative effect (36), sustained by its plasma half-life of 10 hours.	Ib
Dopamine Antagonists *Chlorpromazine:* Used with good success in severe hyperemesis and in hospitalised patients respectively. However, there are only few data showing efficacy and safety in NVP. Neuroleptic drug with sedative effect! The teratogenicity potential has not been proven in studies (30); however, many years of experience indicate no teratogenic effects (37-42).	IIa/III III
Domperidone: The efficacy in the treatment of NVP is not studied. Available data show no increased risk for malformations (43, 44). It should not be used to treat NVP.	III
Metoclopramide: Reduces nausea and vomiting in pregnancy, but its efficacy in the treatment of HG is inferior if compared with other substances (45-47). Cave adverse drug reactions (ADR): dry mouth, extrapyramidal disorders, psychiatric disorders; do not use in pregnant women with depression! Is considered safe during pregnancy (48-50). Newer data, however, show an increased risk for MCM (35).	Ia/III III
Serotonin Antagonists *Ondansetron*: For several years, the use of ondansetron during pregnancy was thought to be safe regarding its teratogenic potency. Ondansetron vs. metoclopramide is non-inferior in regard to its efficacy against nausea and even superior in the treatment of emesis in pregnancy (45). Since 2018 there has been increasing evidence that the teratogenic risk is increased when taken during the 1st trimester: increased risk of cleft palate in the National Birth Defects Prevention Study as well as an increased risk of renal agenesis / - dysgenesis in the Slone Birth Defects Study (51) has been shown. Additionally, a higher risk for ventricular septal defect after exposure of the fetus in the first trimester is discussed (52). In contrast to these results, the data from a US cohort study (2000-2014) with over 1 million women shows at least not a generally increased risk of major malformations (53), additionally, confounding by diagnosis may not absolutely be excluded (54).	IIb
***Corticosteroids (Hydrocortisone, (*Methyl)prednisolone)** The efficacy of corticosteroids compared with placebo or promethazine or metoclopramide has been evaluated in 3 RCT 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 day 2; 71.6% vs 51.2% at day 3; 95.8% vs 76.6% at day 7 [n = 40, P < .001]) (27). Methylprednisolone is not problematic for the embryo/fetus due to inactivation by metabolizing placental enzyme 11beta-hydroxysteroid dehydrogenase type 2 (HSD2).	Ia
Dosage • Pyridoxine (Vitamin B6): 10-25 mg every 8 h p.o.; 200 mg / d i.v. • Ginger (Zintona®): 4x 250 mg /d p.o. • Meclozine/Pyridoxine/Caffeine (Itinerol B6®): Max. 4x 25/25/25 mg /d p.o.; 2x 50/50/20 mg suppositories rectally • Doxylamine/Pyridoxine (Cariban®): Max. 4x 10/10 mg /d p.o. • Chlorpromazine (Largactil® (Import)): 2x 13 mg /d p.o. or i.v. • Metoclopramid (Paspertin®, Primperan®): max 3x 10 mg /d p.o. or i.v. • Ondansetron (Zofran®): 2x 4-8 mg /d p.o. or i.v. • Methylprednisolone (Solu-Medrol®): 2x 125-250 mg /d i.v.	
Prevention In case of a subsequent pregnancy, 2 studies suggest that early or preconception multivitamins and mineral preparation reduce the incidence of NVP. (55, 56). Although there is no trial data, preconceptual counseling can provide information and reassurance to a woman previously affected by NVP and HG. It also allows planning for early effective management if symptoms of NVP and HG occurs (57). .	IIb IV
Summary and Recommendations: - **NVP is very common (50-80%) during pregnancy. Severe vomiting (HG) occurs in 0.3-3%** - **Maternal and fetal complications are higher with HG** - **Women should be assessed for NVP at each visit during early pregnancy. The PUQE 24 score can be helpful for quantification of NVP symptoms** - **Treatment should start with dietary measures, alternative treatments and vitamins.** - **If symptoms persist, pharmacologic treatment using antihistamines as first choice medication should be initiated** - **Treatment focus should be on reducing symptoms, improving quality of life, preventing serious complications and minimizing fetal effects of pharmacologic treatment.** - **An early and stepwise approach is recommended according to the attached algorithm**	

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

Guideline RCOG Nr. 44, 2006

References with the authors

Conflict of interest declaration:

BMT,IH and MH have participated in advisory boards and/or given lectures sponsored by EFFIK
DS: Advisory Board and Lecture for EFFIK (fees in favour of clinic research fund)