**AN ADAPTED EVIDENCE-BASED CLINICAL PRACTICE GUIDELINE**

**ON**

**NAUSEA & VOMITING OF PREGNANCY & HYPEREMESIS GRAVIDARUM**

**Overview**

This is an adapted evidence-based clinical practice guideline for nausea and vomiting of pregnancy and hyperemesis gravidarum.

**Guideline adapter**

**This guideline has been adapted by the Egyptian Universities Obstetrics & Gynecology Guideline Working Group (EUOBGYN-GWG).**

**Release date**

July 2023

**GUIDELINE ADAPTATION METHODOLOGY**

This guideline was produced in accordance with the ADAPTE methodology and procedure for the adaptation of evidence-based clinical practice guidelines published by the ADAPTE Group (Fervers B, et al., Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. Int J Qual Health Care 2006; 18(3): 167-176).

**sources of the guideline**

**This guideline was adapted from:**

1. SOMANZ Guideline for Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum (2019). Society of Obstetric Medicine of Australia and New Zealand.  
   <https://www.somanz.org/content/uploads/2020/07/NVP-GUIDELINE-1.2.20-1.pdf>
2. ACOG: Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 189: Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2018 Jan;131(1):e15-e30
3. RCOG Green-top Guideline No.69 (2016). The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum. <https://www.rcog.org.uk/media/y3fen1x1/gtg69-hyperemesis.pdf>
4. Campbell K, Rowe H, Azzam H, Lane CA. The Management of Nausea and Vomiting of Pregnancy. J Obstet Gynaecol Can. 2016 Dec;38(12):1127-1137.

# Introduction

* Nausea and vomiting of pregnancy (NVP) are common conditions that affect the health of a pregnant woman and her fetus. NVP affect 90% of pregnant women in Egypt. They diminish a woman’s quality of life and contribute to health care costs and time lost from work.
* The woman’s perception of the severity of her symptoms plays a critical role in the decision of whether, when, and how to treat NVP
* NVP should be distinguished from nausea and vomiting related to other causes.
* Electrolyte, thyroid, and liver abnormalities may be present.
* Hyperemesis gravidarum (HG) is the most common indication for admission to the hospital during the first part of pregnancy, and is second only to preterm labor as the most common reason for hospitalization during pregnancy, affecting 0.5-2% of all pregnant women in Egypt.
* From an epidemiologic perspective, HG appears to represent the extreme end of the spectrum of NVP.

# Initial Clinical Assessment and Baseline Investigations

**History**

* Nausea, vomiting, hyper-salivation, spitting, loss of weight, inability to tolerate food and fluids, effect on quality of life.
* NVP/HG in a previous pregnancy.
* Exclude other causes:
  + Chronic *Helicobacter pylori* infection, gastro-esophogeal reflux disease (GERD), abdominal pain, urinary symptoms, infection, drug history
* A history of a chronic condition associated with nausea and vomiting that predates pregnancy should be sought (e.g., cholelithiasis or diabetic gastroparesis).
* Quantify severity using PUQE score (Table 1): Assesses the severity of nausea and vomiting with three questions relating to duration of nausea, and frequency of vomiting and dry retching symptoms.

**Physical Examination**

* Temperature, pulse, blood pressure, Oxygen saturation, respiratory rate, abdominal examination, weight, signs of dehydration, signs of muscle wasting, other examination as guided by history.

**Table 1. Modified Pregnancy-Unique Quantification of Emesis and Nausea**

**Circle the answer that best suits your situation from the beginning of your pregnancy.**

**1. On average in a day, for how long do you feel nauseated or sick to your stomach? Not at all 1 hr or less 2–3 hr 4–6 hr More than 6 hr**

**(1) (2) (3) (4) (5)**

**2. On average in a day, how many times do you vomit or throw up?**

**7 or more times 5–6 times 3–4 times 1–2 times Zero**

**(5) (4) (3) (2) (1)**

**3. On average in a day, how many times do you have retching or dry heaves without bringing anything up?**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **None** | **1–2 times** | **3–4 times** | **5–6 times** | **7 or more** |
| **(1)** | **(2)** | **(3)** | **(4)** | **(5)** |

**Total score (sum of replies to 1, 2, and 3): mild NVP, 6 or less; moderate NVP, 7–12; severe NVP, 13 or more.** **NVP = Nausea and vomiting of pregnancy.**

# Role For Laboratory or Radiologic Assessment in The Diagnosis of Hyperemesis Gravidarum

**Ultrasound examination**

* May identify a predisposing factor such as multiple gestation or molar gestation.
* Abdominal ultrasound examination to evaluate gastrointestinal causes.

**Common laboratory abnormalities**

* Elevated liver enzymes (AST and ALT, usually less than 300 units/L),
* Elevated Serum bilirubin (less than 4 mg/dL),
* Elevated Serum amylase and/or lipase concentrations (up to five times greater than normal levels).

# Differential Diagnosis

* **Gastrointestinal conditions**
* Gastroenteritis, gastroparesis, achalasia, GERD, peptic ulcer disease, *Helico bacter pylori*, biliary tract disease, hepatitis, intestinal obstruction, pancreatitis.
* **Conditions of the genitourinary tract**
* Pyelonephritis, uremia, ovarian torsion, kidney stones, degenerating uterine leiomyoma.
* **Metabolic conditions**
* Diabetic ketoacidosis, porphyria, Addison’s disease, hyperthyroidism, hyperparathyroidism.
* **Neurologic disorders**
* Pseudotumor cerebri, vestibular lesions, migraines, tumors of the central nervous system, lymphocytic hypophysitis.
* **Miscellaneous conditions**
* Drug toxicity or intolerance, psychological conditions.
* **Pregnancy-related conditions**
* Acute fatty liver of pregnancy, preeclampsia.

# Management Of NVP And HG

The majority of women with a PUQE-24 score <13 can be managed in outpatient clinic. Ambulatory Day Stay facilities should be utilized for women who require parenteral fluid resuscitation and parenteral anti-emetic administration if they are unable to tolerate these orally drugs at home.

**Hospitalization is indicated** for women with severe NVP or HG (PUQE score ≥13) or the following high-risk group:

* Severe electrolyte disturbance, e.g., potassium < 3.0 mmol/L
* Significant renal impairment or acute kidney injury: creatinine > 1.5 mg/dL
* Concurrent significant co-morbidity, e.g., Type 1 diabetes, poorly controlled epilepsy, transplant recipients, or those requiring essential immunosuppression
* Malnutrition/continuing significant weight loss despite therapy or starvation ketoacidosis
* Associated conditions requiring inpatient management, e.g., infection, hematemesis

**Non-pharmacological therapy (First Line Therapy)**

* Modification of working patterns, exercise, daytime sleeps and an earlier bedtime.
* Eating small, more frequent meals that are low in fat.
* Avoiding spicy or fatty foods, avoiding drinking cold or sweet beverages, avoiding strong odors.
* Eating bland or dry foods, high-protein snacks, and crackers in the morning.
* Ginger has shown some beneficial effects in reducing nausea symptoms and can be considered as a non-pharmacological option.
* Discontinue iron-containing prenatal vitamins during the first trimester and substitute them with folic acid.

**Pharmacological therapy (Second Line Therapy)**

Women who have nausea and vomiting but are not dehydrated can be managed in the community with oral antiemetic, support, reassurance, oral hydration and dietary advice.

In mild-moderate NVP:

* Start with ginger ± vitamin B6.
* Add oral antihistamine or dopamine antagonist if needed.

In moderate-severe NVP or inadequate response to initial treatment:

* Consider IV/IM antihistamine or dopamine antagonist.
* Excessive sedation or inadequate response: add /substitute oral serotonin
* antagonist at least during daytime
* Add acid suppression therapy

In refractory NVP or HG:

* Intensify acid suppression
* Consider corticosteroids in addition to other antiemetics
* Manage/prevent constipation with laxatives

**Vitamin B6 (Pyridoxine) With or Without Doxylamine**

Considered first-line pharmacotherapy. The combination of vitamin B6 (pyridoxine) (10 mg) plus doxylamine (10 mg) has FDA approval. The standard recommended starting dose is 4 tablets a day. However, a review of the safety of doxylamine /pyridoxine taken in doses as high as 5 to 12 tablets a day has been reported. Treatment should be tapered rather than stopped at once.

**Antihistamines**

Doxylamine is an H1 receptor antagonist that has been shown to be safe and effective in the treatment of NVP. Other Antihistamines (such as dimenhydrinate and diphenhydramine) have common adverse effects including sedation, dry mouth, lightheadedness, and constipation.

**Dopamine Antagonists**

Metoclopramide and various phenothiazine medications (prochlorperazine, or chlorpromazine): These medications may be given orally, rectally, intramuscularly, or intravenously, but the rates of drowsiness, dizziness, and dystonia were less with metoclopramide use. Adverse effects of these medications include dry mouth, drowsiness, dystonia, and sedation.

**Serotonin 5-hydroxytryptamine type 3 receptor antagonists**

Evidence is limited on the safety or efficacy of the serotonin 5-HT3 inhibitors (e.g., ondansetron, granisetron) for nausea and vomiting of pregnancy; however, their use appears to be increasing. Common adverse effects of ondansetron include headache, drowsiness, fatigue, and constipation. Ondansetron can prolong the QT interval, especially in patients with underlying heart problems, hypokalemia, or hypomagnesemia.

**Steroids**

Several case series have suggested a benefit of corticosteroids in the treatment of hyperemesis gravidarum.

Corticosteroids should be avoided during the first trimester because of possible increased risk of oral clefting and should be restricted to refractory cases.

**Adjuvant therapy**

* **Gastro-oesophageal reflux therapies**

Antacids containing magnesium, calcium, or aluminum are used in pregnancy as first-line treatment for reflux. There is no evidence of teratogenic effect in the recommended doses.

Antacids containing bicarbonate **should be avoided** in pregnancy because they may cause metabolic alkalosis and fluid overload in both mother and fetus.

H2 receptor antagonists, including cimetidine, and famotidine, are the most commonly used drugs to manage reflux when antacids are not effective.

* **Laxatives and stool softeners**

Dehydration, gastric dysrhythmia and other drugs used for treatment of NVP, particularly ondansetron, can contribute to significant and symptomatic constipation in women with NVP and HG. Increasing dietary fiber and fluids is the preferred treatment of constipation during pregnancy. For refractory cases, occasional use of magnesium salts or lactulose is considered suitable for use in pregnancy.

* **Intravenous fluid and parenteral feeding**

Used for correction of dehydration in women with NVP or HG associated dehydration and electrolyte disorders.

* **Enteral and parenteral nutrition**

HG leads to dehydration, fluid and electrolyte abnormalities, and inadequate nutrition in severe cases. Dextrose and vitamins should be included in the therapy when prolonged vomiting is present, and thiamine should be administered before dextrose infusion to prevent Wernicke encephalopathy. Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as the first-line treatment to provide nutritional support to the woman with hyperemesis gravidarum who is not responsive to medical therapy and cannot maintain her weight.

# Summary of Recommendations

**6.1. The following recommendations are based on good and consistent scientific evidence**

**(Level A)**

Treatment of nausea and vomiting of pregnancy with vitamin B6 (pyridoxine) alone or vitamin B6 (pyridoxine) plus doxylamine in combination is safe and effective and should be considered first- line pharmacotherapy.

The standard recommendation to take prenatal vitamins for 1 month before fertilization may reduce the incidence and severity of nausea and vomiting of pregnancy.

The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis, or hyperemesis gravidarum, or both, includes supportive therapy, and antithyroid drugs are not recommended.

**6.2. The following recommendations are based on limited or inconsistent scientific evidence**

**(Level B)**

Treatment of nausea and vomiting of pregnancy with ginger has shown some beneficial effects in reducing nausea symptoms and can be considered as a non-pharmacologic option.

Treatment of severe nausea and vomiting of pregnancy or hyperemesis gravidarum with methylprednisolone may be efficacious in refractory cases; however, the risk profile of methylprednisolone suggests it should be a last-resort treatment.

**6.3. The following recommendations are based primarily on consensus and expert opinion**

**(Level C)**

Early treatment of nausea and vomiting of pregnancy may be beneficial to prevent progression to hyperemesis gravidarum.

Intravenous hydration should be used for the patient who cannot tolerate oral liquids for

a prolonged period or if clinical signs of dehydration are present.

Correction of ketosis and vitamin deficiency should be strongly considered. Dextrose and vitamins should be included in the therapy when prolonged vomiting is present, and thiamine should be administered before dextrose infusion to prevent Wernicke encephalopathy.

Enteral tube feeding (nasogastric or nasoduodenal) should be initiated as the first-line treatment to provide nutritional support to the woman with hyperemesis gravidarum who is not responsive to medical therapy and cannot maintain her weight.

Peripherally inserted central catheters should not be used routinely in women with hyperemesis gravidarum given the significant complications associated with this intervention. Peripherally inserted central catheters should be utilized only as a last resort in the management of a woman with hyperemesis gravidarum because of the potential of severe maternal morbidity.