HYPEREMESIS GRAVIDARUM

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1. DEFINITIONS

- **Nausea and vomiting in pregnancy** (50-90% of pregnant women)
  Isolated nausea and vomiting are a very common symptom in the first trimester of pregnancy. They generally present in a mild form (1-2 vomits a day) with correct tolerance to intake. They usually appear before 9 weeks of pregnancy and disappear at around 16 weeks in 90% of women.
- **Hyperemesis gravidarum (0.5-2% of pregnant women)**
  Hyperemesis gravidarum (HG) constitutes the most severe spectrum of nausea and vomiting in pregnancy, in which vomiting persists throughout the day and intolerance to food intake is added. In addition, this situation entails the presence of a series of obvious physical and analytical signs, such as weight loss, dehydration and hydroelectrolytic changes. The diagnosis is always one of exclusion (absence of other pathologies that explain the symptoms).

2. AETIOLOGY OF NAUSEA AND VOMITING DURING PREGNANCY

Although the aetiology of HG is unknown, different causes have been proposed:

1. **Elevated levels of beta-hCG**. hCG has a very similar in structure to TSH, so the peak of the beta-hCG level (usually seen around 12 weeks of pregnancy) can lead to transient hyperthyroidism and thus symptoms of hyperemesis. This hypothesis would explain the higher incidence in women with trophoblastic disease or multiple pregnancies.

2. **Family/personal predisposition**. There seems to be a predisposition to develop HG in daughters and sisters of women who presented it during their pregnancies. There is also a greater risk in case of nausea and vomiting in a previous pregnancy. In these patients, preventive measures are recommended, including hygienic-dietary measures (see section 8 and annex 1).

3. DIAGNOSIS OF HYPEREMESIS GRAVIDARUM

The diagnosis of HG is mainly **clinical**: the presence of **several vomits** a day that may or may not be related to meals and that associates (partial or total) **intolerance to intake**. It usually starts during the first weeks of pregnancy (< 16 weeks).

The diagnosis of HG will always be one of exclusion. To do this, we will rule out other causes of nausea and vomiting, which will be associated with other clinical signs such as fever, abdominal pain (with the exception of mild hypogastric discomfort), neurological signs (headache, motor disturbances, etc.), palpable goitre, etc. Table 1 summarises the different entities with which to carry out the differential diagnosis together with the key sign to differentiate them.

Table 1: Differential diagnosis

	Differential diagnosis	**Key signs and symptoms for suspicion**
GASTROINTESTINAL	Gastroenteritis, Cholecystitis, Pancreatitis, Appendicitis, Peptic ulcer, Hepatitis, Intestinal obstruction, Gastroparesis, Achalasia	- Abdominal pain (VAS > 7) - Abdominal distension - Transaminitis (> 1000 IU/l), Jaundice - Vomiting related to ingestion only
GENITOURINARY	Pyelonephritis, Renal colic, Uraemia, Adnexal torsion, Fibroid degeneration	- Positive kidney punch test - Altered urinary sediment - Suggestive ultrasound
ENDOCRINOLOGICAL	Diabetic ketoacidosis Gestational hyperthyroidism Hyperthyroidism secondary to Grave's disease	- Elevated capillary glycaemia - Polyuria/polydipsia - Palpable goitre - Analysis with compatible thyroid profile, presence of TSI antibodies - Insomnia, nervousness, hypertension, heat intolerance, exophthalmos
NEUROLOGICAL	Migraine, pseudotumor cerebri, Vestibular lesions (Labyrinthitis, Meniere's disease), Central Nervous System tumour	- Severe headache with other severity criteria - Projectile vomiting
PHARMACOLOGICAL	Opioids	- History of drug abuse
EATING DISORDERS	Anorexia nervosa, bulimia	- Extreme BMI - Inadequate weight gain - Refusal to talk about weight or intake

Abbreviation: VAS, visual analogue scale. TSI, thyroid-stimulating immunoglobulin. BMI, body mass index.

4. MANAGEMENT OF THE PATIENT WITH NAUSEA AND VOMITING IN THE EMERGENCY DEPARTMENT

In any patient consulting with HG symptoms, we should carry out an anamnesis and a basic physical examination. Depending on the severity of the condition, different complementary tests will be performed, following the next diagnostic steps:

4.1 FIRST DIAGNOSTIC STEP:

- **Anamnesis** addressed to determine:
  - Frequency and intensity of symptoms: use the "PUQE Scale" (Table 2).
  - Tolerance to solid and liquid intake. Duration in case of intolerance.

***Table 2**: Severity Scale: PUQE (Mother risk Pregnancy-Unique Quantification of Emesis and Nausea)*

	1. On average, for how long do you feel nauseated or sick to your stomach in a day?			
Never (1)	≤ 1 hr (2)	2-3 hr (3)	4-6 hr (4)	> 6 hr (5)
	2. On average in a day, how many times do you vomit or throw up?			
None (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	≥7 times (5)
	3. On average in a day, how many times do you retch or have dry heaving without bringing anything up?			
None (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	≥7 times (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.***			

Abbreviation: NVP, nausea or vomiting in pregnancy.

- **Basic physical examination:**
  - Rule out signs of dehydration:
    - Tachycardia and hypotension
    - Loss of skin turgor (skin tenting sign)
    - Mucosal dryness
  - Assessment of the consequences of intolerance to solid intake:
    - Capillary blood glucose: significant if blood glucose < 90 mg/dl
    - Ketonuria (urine test strip): significant if ≥ 2+
    - % Weight loss compared to the beginning of pregnancy: relevant if > 5%

- **Differential diagnosis**: a physical examination will be carried out aimed at ruling out other causes of nausea and vomiting: abdominal palpation, neck palpation to rule out goitre and thyroid nodules, neurological examination.

- **Gynaecology-obstetrics ultrasound** to:
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  - Assess the presence of an ongoing evolutive pregnancy
  - Rule out trophoblastic disease
  - Evaluate if singleton/multiple pregnancy

Proceed to the second diagnostic step in the following situations:

- Relevant HG symptoms (PUQE ≥ 7)

- Objective repercussions of HG: dehydration, capillary glycaemia <60 mg/dl or ketonuria ≥ 2+, > 5% weight loss
- Suspected underlying pathology (other than HG)
- Reconsulting with the same symptoms (HG)
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4.2 SECOND DIAGNOSTIC STEP:

- **Basic blood test:** complete blood count, coagulation, serum ionogram, creatinine, urea and venous acid-base balance.
  Interpretation:
  - Complete blood count: assess the degree of haemoconcentration secondary to dehydration, as well as possible vitamin deficiencies:
    - Hematocrit: significant when an increase is detected with respect to previous analysis.
    - Haemoglobin and MCV (Medium Corpuscular Volume): diagnose anaemia if Hb < 11 g/dl in the first trimester. Anaemia is considered to be secondary to a folic acid or vitamin B12 deficiency when the MCV > 100 fl (See Anaemia in Pregnancy Protocol).
  - Renal function tests will be useful for assessing hypovolaemia secondary to dehydration.
    - Creatinine and urea: significant when > 1.5 times the normal value.
  - Serum ionogram and venous acid-base balance: to assess whether there is a hydroelectrolytic alteration secondary to vomiting. Of the hydroelectolytic alterations, the most frequent is hypokalaemia (K+ < 3.5 mEq/L). It is produced by renal losses due to associated metabolic alkalosis.
    - Hypokalaemia and hypochloraemia: K^+ < 3.5 mEq; Cl^- < 100 mEq.
    - Metabolic alkalosis: pH > 7.45; $HCO3^-$> 26 mmol/L; pCO2 > 53 mmHg; Anion GAP increased; Base Excess > +3.
    - Coagulation: PT (Prothrombin Time) and aPTT (activated Partial Thromboplastin clotting Time). HG can alter PT due to malabsorption.

- **Extended blood test** in the following situations:
  - High suspicion of underlying pathology other than HG
  - Those patients who meet admission criteria (See Table 3)
  - Inflammation marker: CRP (C-Reactive Protein).
  - Liver function tests:
    - AST/ALT/Bilirubin/LDH: elevation of AST/ALT < 300 IU/l or bilirubin < 4 mg/dl. If higher levels, perform differential diagnosis with gastrointestinal disorders.
  - Pancreatic profile:
    - Amylase/lipase: moderate elevation of amylase/lipase (elevation < 5 times above normal values). If > 5 times above normal levels, suspect an underlying pancreatic disorder.
  - Thyroid profile:
    Especially in the event of signs/symptoms suggestive of hyperthyroidism (goitre or thyroid nodules, exophthalmos, hypertension, tachycardia or palpitations, nervousness, heat intolerance, insomnia, etc.).
    Always in case of hospital admission.
    - TSH and T4: the presence of TSH < 0.1 mU/L (normal TSH in first trimester: 0.1-2.5 mU/L) will be diagnostic of primary hyperthyroidism. It will be subclinical when the free T4 levels are normal (normal free T4 in first trimester: 5-12 mg/dl) or clinical when T4 >12 mg/dl in the first trimester. The most probable cause of this alteration is pregnancy thyrotoxicosis, a situation secondary to the increase in hCG and therefore related to HG. However, if the symptoms are severe or the degree of

analytical alteration is significant, it will be considered to rule out concomitant Graves' disease.

Depending on the results, we will classify the condition as (see table 3):

- Mild-Moderate: outpatient management
- Severe: hospitalisation

***Table 3**: HG classification according to severity – Admission criteria*

MILD-MODERATE	**SEVERE**
ALL the following criteria: - PUQE 3-12 - Liquid intake tolerance - No signs of dehydration - < 5% weight loss - Normal renal tests and ionogram **OUTPATIENT TREATMENT**	ANY of the following criteria - PUQE ≥ 13 - Intake intolerance, even to liquids - Signs of dehydration - Renal or ionic tests alteration - > 5% weight loss - Failure of conservative treatment in full doses **HOSPITALISATION**

5. TREATMENT

Nausea and vomiting in pregnancy is a disease with different spectrums of severity of progressive onset. That is why we must add treatments in stages as the symptoms worsen.
We must start early first-line treatment in symptomatic patients who consult, as well as recommend the preventive measures described in point 8 and annex 1.

5.1 OUTPATIENT TREATMENT
Patients with mild-moderate symptoms of hyperemesis will be eligible for outpatient treatment.

A. FIRST LINE

- **Hygienic-dietary recommendations** (provide information sheet of hygienic-dietary recommendations for pregnant women – Annex 1-).

- Treatment of choice: begin with **Doxylamine 10 mg (antihistamine H1 antagonist) + Pyridoxine 10 mg (vitamin B6)** (FDA A):
  - Recommended dose: 1 tablet/6-8 h orally. Maximum 2 tablets/8 h.
  - If the symptoms persist in a certain time period, increase the immediately preceding dose (e.g. if morning nausea and vomiting persist, increase the evening dose).
  - Side effects: drowsiness and tiredness (28% of patients).

- Other recommendations:
  - **Possibility of adding Ginger**:
    - Recommended dose: 100 mg of ginger extract orally before main meals. It has been shown in randomised clinical trials to improve nausea, but not to reduce vomiting.
  - Suspend oral iron supplementation while the symptoms of hyperemesis persist. In the case of a patient with criteria for anaemia and the need for supplementation, consider changing the iron supplement to a non-ferrous form.
  - **Folic acid supplementation 5 mg/day** for at least 2 weeks or up to 12 weeks.
  - Tell the patient that if there is no improvement in 48-72 h or there is clinical worsening, she should go back to the emergency room for reassessment.

B. SECOND LINE
Continue with second-line outpatient treatment if there is no improvement within the first 48 hours (always after having ruled out severity criteria, Table 3). The addition of the following treatments will be considered:

- First choice: add **Dimenhydrinate - antihistamine H1 antagonist** (FDA B):
  - Recommended dose: 50-100 mg/4-6 h orally. Maximum dose: 400 mg/day (200 mg/day if added to doxylamine).
  - Side effects: drowsiness, headache, dizziness, blurred vision and urinary retention.

- **Diphenhydramine - antihistamine H1 antagonist** (FDA B): as an alternative to dimenhydrinate
  - Recommended dose: 50 mg/6-8 h orally.
  - Side effects: drowsiness, dry mouth and constipation.

- Consider adding **Metoclopramide - Dopamine antagonist** (FDA B):
  - Recommended dose: 5-10 mg/8 h orally. Ideally for occasional or short-term use due to the risk of extrapyramidal side effects: maximum 5 days and maximum 30 mg/day.
  - Side effects: dry mouth and drowsiness. It is associated with extrapyramidal symptoms in some patients (face, neck and tongue spasms), which is why it should be used as second-line therapy.

If the patient presents with epigastric pain or symptoms of gastroesophageal reflux, one of the following may be added to the treatment:

- **Almagate** (FDA B): 1 g/8 h, preferably 30 minutes - 1 hour after the main meals.

- **H2 receptor antagonists**:
  - **Famotidine** (FDA B) 20 mg/12 h orally.
  - If the symptoms of gastroesophageal reflux do not disappear despite the above treatments, add **proton pump inhibitors: Pantoprazole** (FDA B) 20 mg/24 h orally.

!!! RANITIDINE will not be used (oral or IV). European Medicines Agency (EMA) confirms the recommendation to suspend all ranitidine medicines in the EU.
On 17 September 2020, EMA's Committee for Medicinal Products for Human Use (CHMP) confirmed its recommendation to suspend all ranitidine medicines in the EU due to the presence of low levels of an impurity called N-nitrosodimethylamine (NDMA).

5.2 HOSPITALISATION
In severe cases (see Table 3) or in moderate cases where the symptoms persist despite second-line treatment at full doses, a hospital admission for intravenous rehydration and intravenous pharmacological treatment will be necessary.
In patients who require hospital admission, consider evaluation by the Psychiatry service. This applies particularly in women with mental health factors that may influence the maternal symptoms or in cases of anxious-depressive symptoms as a consequence of the discomfort produced by the hyperemesis.

A. FIRST LINE

- **Fasting** for 24-48 h, and reassess according to evolution
- Add **thiamine** (vitamin B1) injectable supplements if vomiting persists more than 3 weeks. It is recommended to prevent Wernicke's encephalopathy, a rare but serious complication.
  - Recommended dose: 100 mg single IV dose with the first saline. Subsequently 100 mg/24 h intravenous (add to saline) for 2-3 days. Administer after the antiemetic and before the glucose solution.
- **Intravenous fluid therapy**: Glucose 10% w/v solution 500 ml/8 h alternated with a crystalloid (Ringer's Lactate) or normal saline 500 ml/8-12 h.
  - If there is **hypokalaemia** (K^+ < 3.5 mEq/L), administer KCl along with the fluid therapy. In this case, this will be added to Glucose 10% w/v solution. As KCl is a medication with potentially serious side effects, the following considerations should be taken into account in the intravenous correction of K^+:
    - Before starting KCl, an ECG will be performed.
    - Recommended dose: 1 mEq/kg/day of KCl every 8 h (10 mEq of K^+ per vial).
    - Very important: **DO NOT exceed 100 mEq/day and do it always in SLOW INFUSION** (never exceed the speed of 10 mEq/hr, since it is a potentially harmful medication that can cause or exacerbate heart conditions, in addition to causing local irritation).

  * As the patient's oral intake tolerance improves, if there is a need for correction of hypokalaemia, this will be done with oral supplementation (go to point 7).

- **Metoclopramide - Dopamine antagonist** (FDA B)**:**
  - Recommended dose: 5-10 mg/8 h IV. Ideally for occasional or short-term use due to the risk of extrapyramidal side effects: maximum 5 days and maximum 30 mg/day.
  - Side effects: dry mouth and drowsiness. It is associated with extrapyramidal symptoms in some patients (face, neck and tongue spasms), which is why it should be used as a second-line treatment.

!!! ONDANSETRON will not be used (oral or IV): European Medicines Agency (EMA) PRAC recommendations on signals (8-11 July 2019 PRAC meeting):
Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy. The available epidemiological studies on heart defects show conflicting results.
Ondansetron should not be used during the first trimester of pregnancy.

If a PT < 80% is detected in the admission blood test, treatment with vitamin K1 will be started.

- **Vitamin K1**: 10 mg/ml ampoules every 48-72 h depending on deficiency and until PT > 80% recovery is achieved

If the patient presents with epigastric pain or symptoms of gastroesophageal reflux:

- Add **Pantoprazole 40 mg/24 h IV** (FDA B).

!!! Remember that **RANITIDINE will not be used** (oral or IV)

B. SECOND LINE
Continue with second-line inpatient treatment if, after 48 hours of intensive treatment with the drugs specified as first line in the hospital, severe symptoms persist, with no tolerance to solid intake:

- **Methylprednisolone** (FDA C)
  !!! Its use below 10 weeks is contraindicated due to its association with lip/palate clefts.
- Recommended dose: 16 mg/8 h orally or IV for 3 days, followed by a tapering regimen of oral Prednisone (40 mg/day for 1 day, 20 mg/day for 3 days and 10 mg/day for 3 days).
- If there is no response in the first 3 days, treatment should be interrupted because improvement is not expected.

If, after 5 days of admission and after having exhausted all the previous interventions, the patient has **NULL oral tolerance to solid intake**, it is advisable to consult with the Nutrition service to assess the specific needs of each case (including enteral nutrition through a nasogastric tube vs. parenteral nutrition). In this case, a complete blood analysis will be carried out, including a nutritional profile (sodium, potassium, chlorine, calcium, phosphorus, magnesium, glucose, BUN, triglycerides and proteins, prealbumin and albumin).

6. MANAGEMENT AND CONTROLS DURING HOSPITALISATION

Diet management should be conservative and adapted to the clinical situation of the patient. After a period of fasting without vomiting (generally 24-48 h), the oral intake will be gradually introduced. Generally, it will be based on introducing frequent and small meals (minimum 5 meals). Solid, protein-rich foods will preferably be administered, avoiding spicy and fatty foods. Cold drinks and cold foods are better tolerated (See Annex 1).

Oral MEDICATION:
As oral tolerance to solid intake progresses, the medication can be changed to oral:

- **Antiemetics and antacids** (if needed):
  - **Metoclopramide**, Dopamine antagonist (FDA B): 5-10 mg/8 h orally. Ideally for one-off or short-term use (maximum 5 days), and a maximum of 30 mg/day.
  - **Pantoprazole**, proton pump inhibitors (FDA B): 20 mg/24 h orally.

- Consider maintaining **oral potassium supplementation** if hypokalaemia persists, until normalisation.
  - If there is associated alkalosis: KCl capsules 600 mg (containing 8 mEq of K+ per tablet). Dose: 2-4 capsules/8 h (maximum dose 7200 mg or 12 capsules in 24 h).

  - If there is no associated alkalosis: potassium-ascorbate-aspartate capsules (containing 25 mEq of K+ per tablet). Dose: 40-100 mEq/day, divided into 2-3 doses.

- Consider maintaining **oral vitamin K** if PT persists < 80%, until normalisation.
  - Vitamin K: 10 mg/ml ampoules every 24-48 h orally

- Reintroduce **folic acid supplementation**:
  - Folic acid 5 mg: 1 tablet a day for at least 2 weeks or up to 12 weeks of pregnancy.

ANALYTICAL CONTROLS:

- During hospitalisation, control blood tests will be carried out every 48-72 hours, although this may vary depending on previous analytical findings and evolution during admission.
- As a general rule, include the following: haemogram, ionogram, creatinine, urea, transaminases, bilirubin, LDH and venous acid-base balance.
- Depending on previous results, consider adding the following in the control blood tests: coagulation, pancreatic profile and thyroid profile.
- In the case of an altered thyroid profile, consider including TSI (or TRAb) and anti-TPO antibodies to rule out Graves' disease.

DIURESIS CONTROL:

- A qualitative control of diuresis will be carried out, to rule out signs of dehydration.

FETAL VIABILITY CONTROL:

- An ultrasound will be performed to verify fetal viability at least on admission and prior to discharge.

7. HOSPITAL DISCHARGE

Consider patient discharge if good control of symptoms is achieved during 24-48 hours with oral medication.

Medication and discharge recommendations:

- Prescribe oral medication that allows the improvement and stability of the condition (ideally 1st line treatment).
- Folic acid supplementation 5 mg/day for at least 2 weeks or up to 12 weeks of pregnancy.
- Supplementation with folic acid and/or vitamin B12 if a deficiency has been detected
- Suspend ferrous iron supplementation while the symptoms last.
- Delivery of an information sheet on the "Hygienic-dietary recommendations for pregnant women" (Annex 1)

8. RECURRENCE AND PREVENTIVE MEASURES

The risk of recurrence in patients diagnosed in second pregnancies with HG is 24%. In case of > 2 pregnancies, the risk of recurrence is 11% in all subsequent pregnancies. For this reason, when visiting a patient with a history of HG or with the onset of mild symptoms, we must be especially careful in prevention. There are different proposals that have been shown to reduce the incidence/recurrence of HG. These include:

- **Periconceptional vitamin complexes**. Its administration is recommended, with the exception of iron supplementation.
- **Hygienic-dietary measures**. All pregnant women with a history of HG or upon the appearance of symptoms compatible with HG must be advised on the hygienic-dietary measures listed in Annex 1.

ANNEX 1: Dietary recommendations against nausea and vomiting 1st trimester

Nausea and vomiting are frequent symptoms during the first months of pregnancy. However, an excess of these can cause discomfort. We detailed below some recommendations in order to improve their tolerance to oral intake.

What kind of foods should I avoid?

- Avoid fizzy drinks, irritating beverages (alcohol or caffeine) or acid ones (orange juices).
- Avoid hot drinks. Eat food at room temperature.
- Temporarily exclude foods that trigger your nausea/vomiting.
- Do not eat fatty foods (fried, battered, breaded, sauces).
- Avoid, at first, soupy foods (soups, milk, juices, etc.).

How do I organise the meals?

- Eat several meals a day (5-7 times), in small quantities.
- Start intake with dry foods: crackers, toast, breakfast cereals (sugar-free).
- It is preferable to choose soft foods, steamed, boiled or grilled.
- If the nausea usually occurs at the same time of day, change meal times.
- Rest after meals, at least one hour, sitting or semi-sitting at 45º.

Also remember:

- Eat slowly, chewing food properly in a calm environment.
- Avoid cooking yourself.
- Do not wear tight clothing.
- It is very important that you keep hydrated. To do this, drink in very small amounts: in small sips or with a spoon every 10-15 minutes, throughout the day.

I feel a little better… How do I get my diet back on track?

As nausea and/or vomiting cease, it may be considered to introduce the following gradually:

- Bread, pasta, rice and potatoes are generally well tolerated.
- Vegetables: at first, cook them steamed or boiled with light seasonings (a little oil and a little salt). Subsequently include salads and raw vegetables that are more difficult to digest.
- Fruits can preferably be taken whole, but also in juices. Introduce at the end those that are more acidic (orange, kiwi, tangerine, etc.) and with higher fat content (coconut and avocado).
- Dairy products should initially be skimmed or low in fat (e.g. fresh cheese). As tolerance increases, incorporate those with a higher fat content (whole milk, cheeses with a higher percentage of fat, whole yogurts, dairy desserts, etc.).
- As for meat, fish and eggs, it is preferable to consume lean meats and sausages (beef tenderloin, skinless chicken, chicken or turkey cold cuts and cooked ham), avoiding those that are smelly (e.g. boiled eggs, fish, etc.) and those with a higher fat content (chorizo, lamb, oily fish, fried eggs, etc.).
- Try to have a varied diet.