Nausea and Vomiting of Pregnancy

Jennifer R. Niebyl, MD
Professor and Vice Chair
Department of Obstetrics and Gynecology
University of Iowa College of Medicine
Iowa City, Iowa

I have received consulting fees from Duchesnay USA and Chateauguay Medical Inc., Canada for information about Diclegis®. The only drug FDA approved for use in pregnancy is Diclegis® [delayed release pyridoxine and doxylamine].

Jennifer R. Niebyl, M.D.

Nausea and Vomiting of Pregnancy: Clinical Perspective

Objectives:
- Discuss clinical impact
- Pharmacologic approach to treatment
- Nonpharmacologic approach to treatment

Spectrum of Nausea and Vomiting of Pregnancy

<table>
<thead>
<tr>
<th>25%</th>
<th>25%</th>
<th>50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Nausea Alone</td>
<td>Nausea and Vomiting</td>
</tr>
</tbody>
</table>

May persist throughout the day


Clinical Impact of Nausea and Vomiting of Pregnancy

- ~35% experience clinically significant NVP
- 35% lose work time (mean, 22 hours/woman)
- Job efficiency and attentiveness is reduced
- 25% lose time from housework
- Negative impact on family relationships and mental health
- Cited as reason for an otherwise undesired pregnancy termination

Hyperemesis Gravidarum: Definition and Incidence

- Persistent vomiting
- Weight loss >5%
- Ketonuria
- Electrolyte abnormalities, hypokalemia
- Dehydration—high urine sp g
- Usually requires hospitalization
- Incidence: 3-5/1000


Reported Complications of Hyperemesis Gravidarum

- Wernicke’s encephalopathy
  - Thiamine (B₁) deficiency
- Mallory-Weiss tear
- Splenic avulsion
- Esophageal rupture
- Pneumothorax
- Peripheral neuropathy due to vitamin B₉ and B₁₂ deficiencies


Replacement of Thiamine in Suspected Deficiency

- Wernicke’s encephalopathy
  - At least 3 weeks of persistent vomiting
  - Classic triad: ophthalmoplegia, gait ataxia, confusion
  - Cases reported regularly in last 5 years
  - 14/19 (74%) neurologically abnormal in follow-up
  - Diagnosis frequently missed in general medical practice (diagnosed at autopsy)
    - 100 mg thiamine IV daily for 2 to 3 days
    - Oral or parenteral thiamine 3 mg daily (standard in most multivitamins)


Differential Diagnosis: Persistent Vomiting

**GI**
- Gastroenteritis
- Biliary tract disease
- Hepatitis
- Intestinal obstruction

**GU**
- Ulcer Disease
- Pancreatitis
- Appendicitis

**Metabolic**
- DKA

**Neurological**
- Migraine
- CNS lesions

**Later in Pregnancy**
- Preeclampsia
- Fatty liver

Differential Diagnosis:
Persistent Vomiting

Clues Nausea and Vomiting NOT from Pregnancy

- Fever
- Abdominal pain
- Headache
- Goiter
- Liver enzymes > 300 u/L
- Serum bilirubin > 4 mg/L
- Serum amylase or lipase > 5x normal


Characteristics of the Fundamental Stimulus of Nausea and Vomiting of Pregnancy

- Elaborated by placenta, not fetus
- Onset within 4 weeks of LMP in some patients
- Fully manifest by 10 weeks’ gestation
- May persist until delivery of placenta
- Rapid improvement with removal of placenta
- Diminished in older women and multiparas
- Diminished with smoking
**Nausea and Vomiting of Pregnancy: A Disease of Theories**

**Etiology Unknown**
- Hormonal influences
- Vitamin deficiency
- Not a psychological disorder
- Gastrointestinal dysmotility

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**Conservative Management of Nausea and Vomiting of Pregnancy**
- Avoid odors, triggers
- Avoid fatty, spicy foods
- Omit iron tablets
- Frequent small feedings, fluids between meals
- Bland and dry, high-protein low fat foods
- Crackers at bedside in AM
- Avoid empty stomach
- Multivitamins

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**Protein Meals Reduce Nausea and Gastric Dysrhythmias**
- Protein-predominant meals reduce nausea better than equicaloric carbohydrate and fat meals or noncaloric meals
- Liquid meals decreased gastric dysrhythmias more than solids

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**Clinical Management of Nausea and Vomiting of Pregnancy**
- Large ketones
  - LFTs, amylase, electrolytes, urine S.G.
- Ultrasound
  - Multiple gestation
  - Hydatidiform mole
- IV hydration with multivitamins
- Antiemetics
- Avoid parenteral nutrition
  - 25% PICC line sepsis

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**Hyperemesis Gravidarum and Hyperthyroidism**
- HCG cross reacts with TSH, stimulates the thyroid gland
- TSH suppressed
- Hyperthyroidism spontaneously resolves by 16 weeks
- Treating with PTU does not help the nausea and vomiting
- If free $T_4$ elevated, repeat at 20 weeks

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**Peak Nausea and Vomiting Symptoms and hCG**

Week of Peak Symptoms

hCG = human chorionic gonadotropin.


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Nausea and Vomiting in Pregnancy and Pregnancy Outcomes

- Decreased
  - Miscarriage 0.3
  - Congenital malformations 0.5
  - Preterm births 0.5
  - Adverse pregnancy outcomes
- Increased (only with weight loss)
  - IUGR


Fetal Effects of NVP

<table>
<thead>
<tr>
<th></th>
<th>N/V + Maternal Weight Loss (n=28)</th>
<th>N/V, No Maternal Weight Loss (n=33)</th>
</tr>
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<tbody>
<tr>
<td>Mean birth weight (g)</td>
<td>3064</td>
<td>3558</td>
</tr>
<tr>
<td>Percentile for gestational age</td>
<td>38.1</td>
<td>72.0 (P&lt;0.025)</td>
</tr>
<tr>
<td>&lt;10th Percentile</td>
<td>9 (32%)</td>
<td>2 (6%) (P&lt;0.01)</td>
</tr>
<tr>
<td>Macrosomnia (&gt;4000 g)</td>
<td>0 (0%)</td>
<td>6 (18%) (P&lt;0.025)</td>
</tr>
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Treatment of NVP: Vitamin B_6 (Pyridoxine)

- Sahakian et al.
  - 25 mg (1/2 tab) PO q 8 h or placebo (N=59)
  - ~50% of patients stopped vomiting
  - Severe nausea decreased to mild or moderate
  - No effect on mild nausea
- Vutyavanich et al.
  - 30 mg/d PO vs placebo x 5 d (N=342)
  - Significant decrease in nausea (P<0.008)
  - No. of vomiting episodes reduced (P=0.0552)


Hungarian Periconceptional Multivitamin Trial

- 1000 women randomized to multivitamin or placebo (n = 500 each)
- B_1 1.6 mg; B_6 2.6 mg; B_12 4 µg, Fe 60 mg
- Nausea and vomiting needing physician visit
  - 3% vitamins vs 6.6% placebo
- Nausea and vomiting and vertigo
  - 3.4% vitamins vs 7.4% placebo (P<0.01)
  - “Optimization of nutritional status and metabolism”


Nausea and Vomiting of Pregnancy: Other Vitamins

- Vitamin B_12
  - 25 µg: no antiemetic effect
- Multivitamins
  - Vomiting significantly associated with lack of supplementation before 6th wk of pregnancy
- No correlation between B_6 serum levels and morning sickness


Nausea and Vomiting of Pregnancy: Oral B_6 + Doxylamine (Bendectin®)

- 1983: removed from US market by manufacturer
- Available as Diclectin® in Canada (sustained release)
- FDA approval April 2013 Diclegis®
- Currently available OTC as Unisom® SleepTabs+ vitamin B_6

### Treatment of Nausea and Vomiting of Pregnancy

- Oral $\text{B}_6$ + doxylamine (similar to Diclegis®)
- Vitamin $\text{B}_6$ 50-mg tablets
  - $1/2$ tablet tid
- Doxylamine (Unisom SleepTabs®) 25 mg
  - $1$ tablet q hs; $1/2$ tablet in AM and PM prn
- Lack of teratogenicity


### Nausea and Vomiting of Pregnancy: Oral $\text{B}_6$ + Doxylamine (Bendectin®) (1956-1983)

- Doxylamine succinate and vitamin $\text{B}_6$
- “Best studied human nonteratogen”
- Estimated to have been used by 40% of pregnant women at one time
- No evidence of teratogenicity in 170,000 exposures


### Time-Trend of NVP Hospitalization Rate

Limb Reduction Deformities, and Bendectin Usage (1974-1994, Normalized to 1974-76)

- Medication ($n = 131$) vs. placebo ($n = 128$) for 14 days
- NVP score -4.8 vs. -3.9 ($p = .006$)
- Requested continued use 49% vs. 33% ($p = .009$)
- Improved quality of life 2.8 vs. 1.8 ($p = .005$)
- Days lost from employment 0.92 vs. 2.37 ($p = .06$)


### Efficacy of Delayed Release Doxylamine + Pyridoxine

- Vitamin $\text{B}_6$ (pyridoxine) 10 mg + doxylamine 10 mg
- FDA category A for pregnancy
  - 2 tablets qhs, 1 tablet q am prn
  - 1 tablet q pm prn
- Only FDA approved treatment for NVP


### Antiemetic Drugs

- Antihistamines
- Phenothiazines
- Prokinetic agents
- Serotonin (5-HT$_3$) antagonists
- Corticosteroids
- None are FDA-approved for use in pregnancy except $\text{B}_6$ + doxylamine

### New FDA Pregnancy Drug Categories
- Takes effect June 30, 2015
- A, B, C, D, X replaced by 3 narrative sections
  - Pregnancy, including labor and delivery
  - Lactation
  - Female and males of reproductive potential
- Each section with 3 subsections
  - Risk summary
  - Clinical considerations
  - Data

### Antihistamines Used for Nausea and Vomiting of Pregnancy
- Doxylamine (Diclegis®)
- Dimenhydrinate (Dramamine®)
- Diphenhydramine (Benadryl®)
- Meclizine (Antivert®)
- Hydroxyzine (Vistaril®, Atarax®)
- Cetirizine (Zyrtec®)

### Nausea and Vomiting of Pregnancy: Phenothiazines
- Promethazine (Phenergan®)
- Prochlorperazine (Compazine®)
- Chlorpromazine (Thorazine®)
- Adverse effects: sedation, dystonia, hypotension, dry mouth, extrapyramidal symptoms

### Prochlorperazine Buccal Tablets
- Low oral bioavailability of prochlorperazine tablets
- Decreased absorption due to regurgitation
- 6-mg buccal tablet
- Dose: 1 to 2 tablets
- Well tolerated with less drowsiness and sedation

### Droperidol (Inapsine®)
- Prolonged QT interval on ECG, Category C<br>
- Torsades de pointes—potentially fatal arrhythmia (ventricular tachycardia)
- Deaths reported below standard doses
- All patients need 12-lead ECG before, during, and 3 hours after administration of droperidol

**US FDA Black Box Warning 12/5/2001**


### Nausea and Vomiting of Pregnancy: Metoclopramide (Reglan®)
- Prokinetic agent: increases upper GI motility, lower esophageal sphincter tone
- Dopamine antagonist
- Akathisia (restlessness) side effect
- Serotonin syndrome with SSRI’s

Safety of Metoclopramide (Reglan®) in Pregnancy

- 3,458 women (4.2% of pregnancies) exposed in the first trimester in Israel
- Most exposed for 1-2 weeks
- No increased risk of congenital malformations, low birth weight, preterm delivery, or perinatal death
- Safe for use for nausea and vomiting in pregnancy except if patient on SSRI’s

Promethazine vs. Metoclopramide for Hypermesis

- Promethazine 25 mg IV (76) or metoclopramide 10 mg IV (73) both every 8 hours
- Similar vomiting frequency and well-being scores
- Metoclopramide less drowsiness, dizziness, dystonia
- 3 refusals due to pain at injection site (tissue damage)
  - (FDA black box warning promethazine 2009)
  - Give deep IM, not SC or IV
- Metoclopramide (Reglan) preferred over promethazine (Phenergan)

Nausea and Vomiting of Pregnancy: 5-HT₃ Receptor Antagonists

- Ondansetron (Zofran®)
- Dolasetron (Anzemet®)
- Granisetron (Kytril®)
- Ondansetron (Zofran) efficacy similar to promethazine (Phenergan®), but less sedating

Ondansetron Disintegrating Tablets

- Freeze-dried strawberry-flavored tablets
  - 4 mg and 8 mg
- Rapidly disperses when placed on tongue and is absorbed when swallowed
- Useful in patients who have difficulty swallowing or who do not feel able to drink
- Similar efficacy

Safety of Ondansetron (Zofran)

- No increased malformation risk in initial studies
  - median age at use 8 weeks
- 2013 larger study same Danish registry
  - 903,207 exposures
  - 2 x risk cardiac malformations
- 2014 Sweden 2 x risk cardiac malformations
- 2011 CDC: 2 x increased risk cleft palate

Methylprednisolone

- 16 mg po tid x 3 days, then taper by 4 mg/day x 2 weeks
- Initial study suggested benefit (n = 40) vs. promethazine
- Larger study no difference in rate of rehospitalization compared to placebo (n = 110)
  - All patients received promethazine (Phenergan) 25 mg + metoclopramide (Reglan) 10 mg IV + po prn
- Increased risk CL ± CP before 10 weeks gestation

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Corticosteroids

- No increase in anomalies overall
- Prednisone crosses placenta poorly; fetal levels 10% of maternal levels
- O.R. CL ± CP 4.3; CP 5.3
- Meta analysis: O.R. oral clefts 3.4


Preemptive Treatment of Nausea and Vomiting of Pregnancy

- Women who had experienced severe NVP and/or HG in a previous pregnancy
- Randomized to preemptive treatment compared to treatment only after symptoms occurred
- Vitamin B6 + doxylamine on diagnosis of pregnancy vs. onset of NVP symptoms


Acupuncture in NVP

- Acupuncture: 2 randomized trials
  - n = 33, Sweden, vs. placebo acupuncture (different site and superficial) helped hyperemesis gravidarum
  - n = 55, England, traditional acupuncture vs. sham (blunt cocktail stick over different area and dressing); nausea ± vomiting, outpatients, no difference


Preemptive Treatment of Nausea and Vomiting of Pregnancy

- Dose 2 tablets at bedtime, increase to 4 tablets pm
- Add other antiemetics, ginger, acupressure as needed
- Moderate-severe NVP 15% vs. 39% (p = 0.05)
- 78% resolved vs. 50% (p < 0.002)


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Alternative Therapies: Acupressure

- Neiguan point or pericardium 6 (P6)
Acupressure in NVP

- Sea-Band®, Bioband®—pressure
- 7 randomized controlled trials of P6 stimulation
  - Conflicting results
  - Absence of blinded testing
  - Both groups improved with time
  - Largest study—no effect


Nerve Stimulation P6 Acupuncture Point

- PrimaBella — electrical current emitted
  - Rotate dial to 5 settings
- Patients randomized to active or sham device
- Researchers assessing outcomes not blinded
  - 3 week trial, 95 active device, 92 controls
- Nausea and vomiting less in study group (p = 0.01)
- Weight gain 5.5 lb vs. 2.9 lb controls (p = 0.003)
- Weight gain 77% vs. 54% controls (p = .001)
- Medication use 25% both groups


Alternative Therapies: Ginger

- Randomized double-blind trials
  - 70 outpatients with NVP
    - 250 mg ginger capsules vs placebo qid × 4 d
  - 27 women with hyperemesis gravidarum
    - 250 mg ginger capsules vs placebo qid × 4 d
- Reduced nausea and episodes of vomiting in ginger groups


Vitamin B6 Vs. Ginger

- Randomized trial, identical appearing capsules
  - B6 25 mg tid (n = 145)
  - Ginger 350 mg tid (n = 146)
- No differences between 2 groups at 1 week, 2 weeks, 3 weeks in nausea and vomiting
- Ginger: More belching, heartburn
- No differences in fetal outcome, birth weight, or congenital anomalies


Ginger for NVP

- 6 Double blind RCT’s for efficacy, n = 675
  - 4 showed superiority over placebo
  - 2 showed equivalence to vitamin B6
- 1 observational cohort study, n = 187
  - No significant side effects
  - No adverse effects on pregnancy outcome
  - Avoid use with anticoagulants

When All Else Fails . . .

- IV hydration with dextrose 5%/lactated Ringer’s, 75-125 mL/h + vitamins
  - Replace thiamine before giving dextrose
- Enteral tube feedings
  - May be intolerant due to persistent emesis
- Total parenteral nutrition
  - Reserve for those with significant weight loss


Treatment Algorithm for NVP
Monotherapy
- Vitamin B6 (10-25 mg, 3-4 x/day)
  - Add
  - Doxylamine (12.5 mg 3-4 x/day)
  - Adjust according to severity of symptoms
  - Add
  - Dimenhydrinate PO/PR (not to exceed 400 mg per day; not to exceed 200 mg per day if patient is also taking doxylamine)
  - or
  - Promethazine PO/PR (12.5-25 mg every 4 hours, orally or rectally)
(Add alternative therapies at any time)


No Dehydration

Add any of the following:
- Metoclopramide, 5-10 mg every 8 hours, intramuscularly or orally
- or
- Promethazine, 12.5-25 mg every 4 hours, intramuscularly, orally, or rectally
- or
- Trimethobenzamide, 200 mg every 6-8 hours, rectally


Dehydration

Add any of the following
- Dimenhydrinate, 50 mg (in 50 ml saline, over 20 min) every 4-6 hours, intravenously
- or
- Metoclopramide, 5-10 mg every 8 hours, intravenously
- or
- Promethazine, 12.5-25 mg every 4 hours, IM


Nausea and Vomiting of Pregnancy: Summary

- Etiology still not clear, thus many therapies
- Rule out other pathology
- Dietary alterations
- Vitamin B6 + doxylamine
- Antiemetic drugs
- Alternative remedies

Nausea and Vomiting of Pregnancy Useful Resources

- http://www.hyperemesis.org
- http://www.motherisk.org