

Nausea and Vomiting of Pregnancy

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

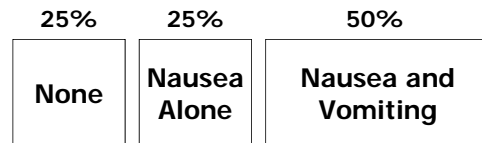
Jennifer R. Niebyl, M.D.

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



May persist throughout the day

Gadsby et al: *Am J Perinatol* 2000;17:207-218.

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

Attard et al: *Am J Obstet Gynecol* 2002;186:S220-S227; Gadsby et al: *Br J Gen Pract* 1993;43:245-248; Mazzotta et al: *J Psychosom Obstet Gynecol* 2000; 21:129-236; O'Brien and Naber. *Birth*. 19:138-143.

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

Bashiri A, Newmann L, Maymon E, et al: *Eur J Obstet Gynecol Reprod Biol* 1995; 63:135-8.

Reported Complications of Hyperemesis Gravidarum

- ◆ Wernicke's encephalopathy
 - Thiamine (B₁) deficiency
- ◆ Mallory-Weiss tear
- ◆ Splenic avulsion
- ◆ Esophageal rupture
- ◆ Pneumothorax
- ◆ Peripheral neuropathy due to vitamin B₆ and B₁₂ deficiencies

Eliakim R, et al: *Am J Perinatology* 2000; 17:207-218.

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)

Gárdián, et al: *Acta Neurol Scand* 1999;99:196-198.

Differential Diagnosis: Persistent Vomiting

GI	Gastroenteritis	Ulcer Disease
	Biliary tract disease	Pancreatitis
	Hepatitis	Appendicitis
	Intestinal obstruction	

Differential Diagnosis: Persistent Vomiting

GU	Pyelonephritis	
<hr/>		
Metabolic	DKA	
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Neurological	Migraine	CNS lesions
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Later in Pregnancy	Preeclampsia	Fatty liver

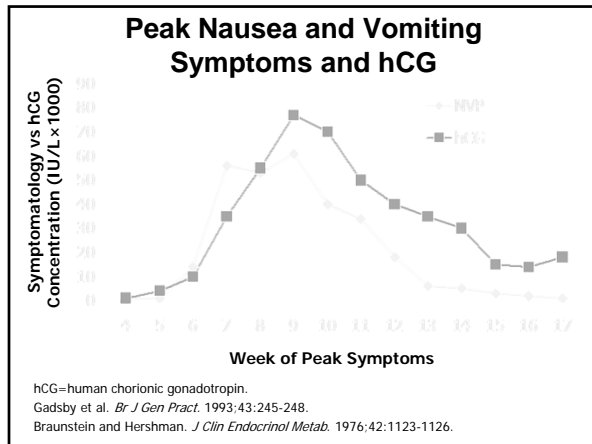
Clues Nausea and Vomiting NOT from Pregnancy

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

ACOG Practice Bulletin #52. *Obstet Gynecol.* 2004; 103:803-814

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

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

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

Jednak et al. *Am J Physiol.* 1999;277:G855-G861.

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

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 T₄ elevated, repeat at 20 weeks

Goodwin TM, et al. *J Clin Endocrinol Metab.* 1992;75:1333-1337.

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

Koren G et al. *Reprod Toxicology* 47 (2014) 77-80.

Fetal Effects of NVP

	N/V + Maternal Weight Loss (n=28)	N/V, No Maternal Weight Loss (n=33)
Mean birth weight (g)	3064	3558
Percentile for gestational age	38.1	72.0 ($P<0.025$)
<10 th Percentile	9 (32%)	2 (6%) ($P<0.01$)
Macrosomia (>4000 g)	0 (0%)	6 (18%) ($P<0.025$)

Gross et al. *Am J Obstet Gynecol*. 1989;160:906-909.

Treatment of NVP: Vitamin B₆ (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 ($P=0.0552$)

Sahakian et al. *Obstet Gynecol*. 1991;78:33-36.
Vutyavanich et al. *Am J Obstet Gynecol*. 1995;173:881-884.

Hungarian Periconceptional Multivitamin Trial

- ◆ 1000 women randomized to multivitamin or placebo (n = 500 each)
- ◆ B₁ 1.6 mg; B₆ 2.6 mg, B₁₂ 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”

Czeizel et al. *Arch Gynecol Obstet*. 1992;251:181-185.

Nausea and Vomiting of Pregnancy: Other Vitamins

- ◆ Vitamin B₁₂
 - 25 µg: no antiemetic effect
- ◆ Multivitamins
 - Vomiting significantly associated with lack of supplementation before 6th wk of pregnancy
- ◆ No correlation between B₆ serum levels and morning sickness

Conklin and Nesbitt. *Obstet Gynecol*. 1958;11:214.
Emelianova et al. *Clin Invest Med*. 1999;22:106-110.
Schuster et al. *Hum Nutr Clin Nutr*. 1985;39:75-79.

Nausea and Vomiting of Pregnancy: Oral B₆ + 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 B₆

Koren et al. *N Engl J Med* 1998; 338:1128-1137.

Treatment of Nausea and Vomiting of Pregnancy

- ◆ Oral B₆ + doxylamine (similar to Diclegis®)
- ◆ Vitamin B₆ 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

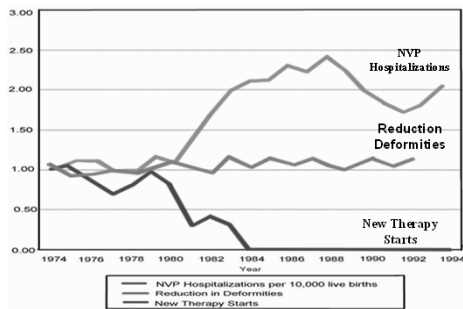
McMahon MJ in Yankowitz J & Niebyl JR: *Drug Therapy in Pregnancy*. Lippincott, Williams & Wilkins, Philadelphia, 2001-p. 81.

Nausea and Vomiting of Pregnancy: Oral B₆ + Doxylamine (Bendectin®) (1956-1983)

- ◆ Doxylamine succinate and vitamin B₆
- ◆ “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

Holmes LB: *Teratology* 1983; 27:277-281.

Time-Trend of NVP Hospitalization Rate, Limb Reduction Deformities, and Bendectin Usage (1974-1994, Normalized to 1974-76)



McKeigue, P. M., Lamm, S. H., Linn, S. and Kutcher, J. S. (1994). Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. *Teratology*, 50: 27-37.

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Efficacy of Delayed Release Doxylamine + Pyridoxine

- ◆ 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)

Koren G, et al: *Am J Obstet Gynecol*. 2010;203:571.

Delayed-Release B₆/Doxylamine

- ◆ Vitamin B₆ (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-HT₃) antagonists
- ◆ Corticosteroids

- ◆ None are FDA-approved for use in pregnancy except B₆ + doxylamine

Koren G: *Am J Obstet Gynecol* 2002; 186:5248-5252.

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

Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling. <https://www.federalregister.gov/articles/2014/12/04/2014-28241>

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

Singh et al. *J Indian Med Assoc.* 1999;97:346-347.

Droperidol (Inapsine®)

- ◆ Prolonged QT interval on ECG, Category C_M
- ◆ 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

Kovac. *Drugs* 2000; 59:213-243 USA FDA MedWatch.

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

Matok I, et al: *N Engl J Med* 2009; 360:2528

Promethazine vs. Metoclopramide for Hyperemesis

- ◆ 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)

Tan, PC, et al: *Obstet Gynecol* 2010; 115:975-81.

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

Einarson AK, et al. *Teratology*. 2002; 65:308.
Sullivan, et al. *Am J Obstet Gynecol* 1996; 174:1565-8.

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

Zofran ODT [product information]. GlaxoSmithKline; 2001.
LeBourgeois et al. *Clin Oncol (R Coll Radiol)*. 1999;11:340-347.

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

Pasternak, B et al: *New Engl J Med* 2013; 368: 814.
Andersen et al: *Int Soc Pharmacoevidemol* 2013, abstract 25.
Anderka, M et al: *Birth Defects Res A Clin Mol Teratol* 2012; 94:22.
Danielsson, B et al: *Reprod Toxicol* 2014; 50:134-137.

Methylprednisolone

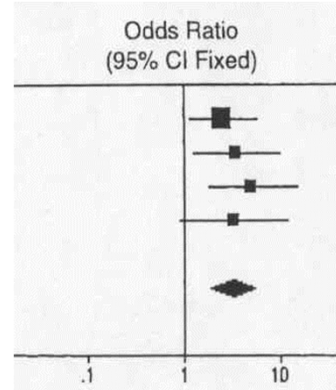
- ◆ 16 mg po tid x 3 days, then taper by 4 mg/day x 2 weeks
- ◆ Initial study suggested benefit (n = 40) vs. promethazine
- ◆ Larger study no difference in rate of re hospitalization compared to placebo (n = 110)
 - All patients received promethazine (Phenergan) 25 mg + metoclopramide (Reglan) 10 mg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

Safari et al: *Am J Obstet Gynecol* 1998; 179:921-924.
Yost NP: *Obstet Gynecol* 2003; 102:1250-1254.
Park-Wyllie et al: *Teratology* 2000; 62:385-392.

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

Carmichael SL: *Am J Med Genet* 1999; 86:242-244.
Park-Wyllie L: *Teratology* 2000; 62:385-392.



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

Maltepe C & Koren G: *Obstet Gynecol Int* Vol. 2013, 2013; Article ID 809787

Preemptive Treatment of Nausea and Vomiting of Pregnancy

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

Maltepe C & Koren G: *Obstet Gynecol Int* Vol. 2013, 2013; Article ID 809787

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

Knight B, et al. *Obstet Gynecol*. 2001;97:184-8.
Christer PO, et al. *J Pain Symptom Man*. 2000;20:273-9.

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

O'Brien et al. *Am J Obstet Gynecol.* 1996;174:708-715.
Dundee et al. *J R Soc Med.* 1988;81:456-457.



PrimaBella

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

Rosen T, et al. A randomized controlled trial of nerve stimulation for relief of nausea and vomiting in pregnancy. *Obstet Gynecol.* 2003;102:129.

Alternative Therapies: Ginger

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

Vutyavanich et al. *Obstet Gynecol.* 2001;97:577-582.
Fischer-Rasmussen et al. *Eur J Obstet Gynecol Reprod Biol.* 1991;38:19-24.

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

Smith C, et al. *Obstet Gynecol.* 2004;103:639-645.

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

Borrelli F, et al. *Obstet Gynecol.* 2005;105:849.

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

Eliakim et al. *Am J Perinatol.* 2000;17:207-218.
Koren and Levichek. *Am J Obstet Gynecol.* 2002;186:S248-S252.

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)

Koren and Levichek. *Am J Obstet Gynecol.* 2002;186:S248-S252.
ACOG Practice Bulletin #52, April 2004, reaffirmed 2009.

Treatment Algorithm for NVP

No Dehydration

Add any of the following:

Add:

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

Koren and Levichek. *Am J Obstet Gynecol.* 2002;186:S248-S252.

Treatment Algorithm for NVP

Dehydration

Add any of the following

Add:

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

Koren and Levichek. *Am J Obstet Gynecol.* 2002;186:S248-S252.

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>
- ◆ ACOG Practice Bulletin #52. *Obstet Gynecol* 2004; 103:803-814, reaffirmed 2009