Hyperemesis Gravidarum

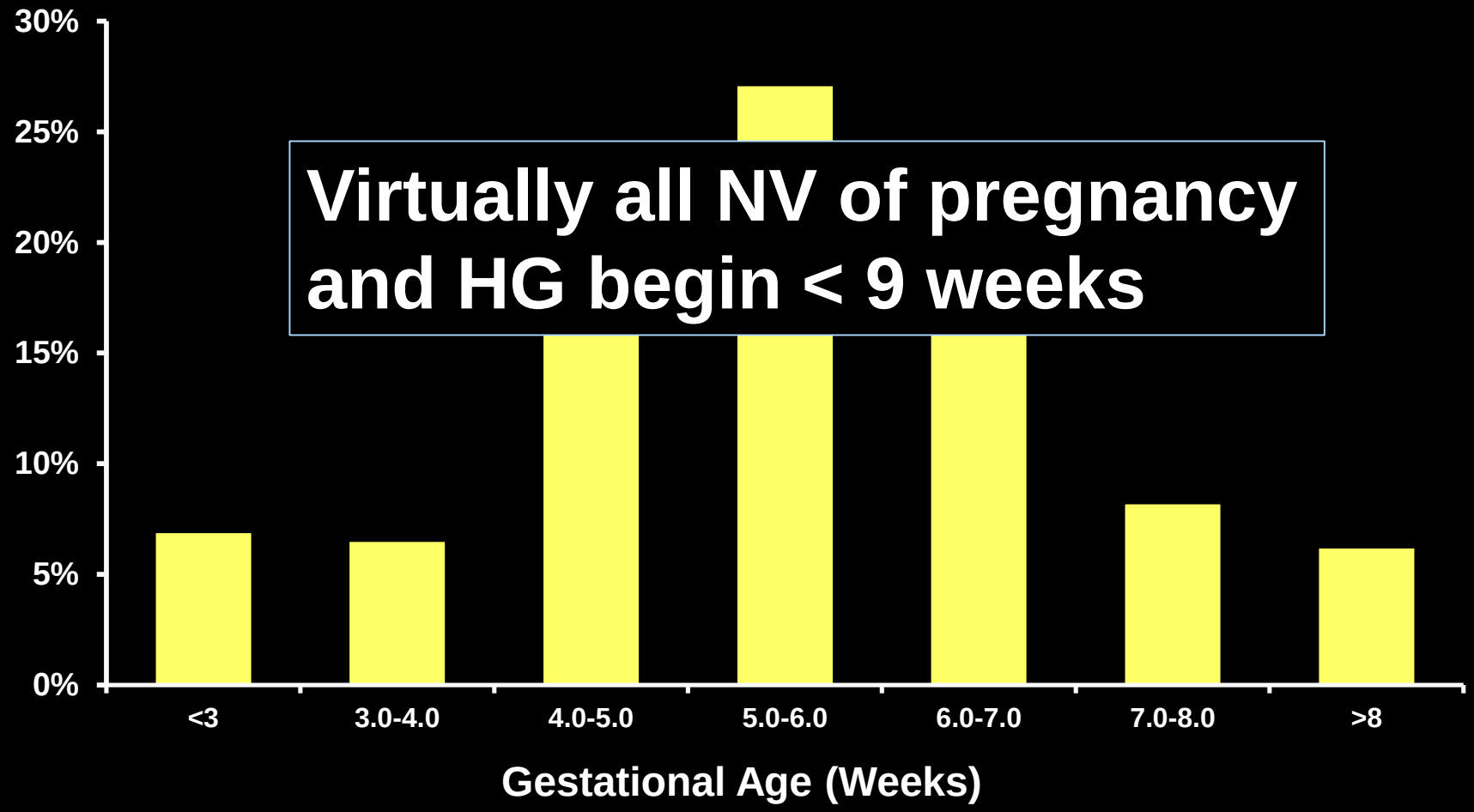
Objectives

- Review nausea and vomiting in pregnancy (NVP
- Recognize pathological nausea and vomiting in pregnancy (hyperemesis gravidarum)
- Be familiar with non-pharmacological and pharmacological treatment

Nausea and Vomiting in Pregnancy

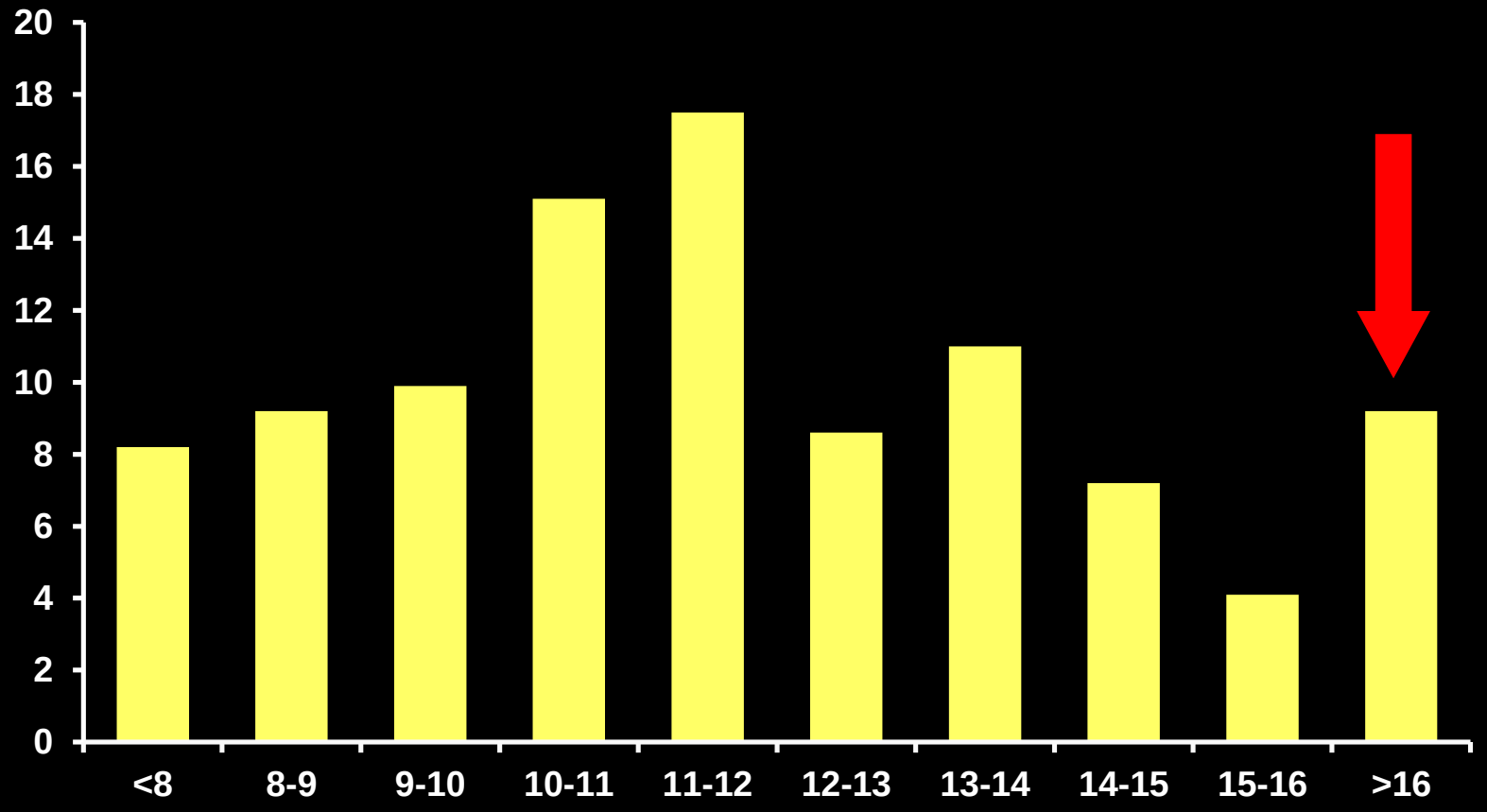
- **Common**
  - No symptoms 25%
  - Nausea alone 25%
  - Nausea and vomiting 50%
- **Disruptive**
  - 35% of women miss work
- **“Morning sickness”**
  - 80% of symptoms last all day
- **Mostly resolves by 20 weeks**

Onset of NVP



Gadsby R, BrJ Gen Prac 43, 1993

Improvement of NVP



Gadsby R, BrJ Gen Prac 43, 1993

Hyperemesis Gravidarum (HG)

- **Extreme NVP**
  - Relatively rare (0.3-3.0% of pregnancies)
- **Definition**
  - Persistent vomiting unrelated to other causes
  - Signs of starvation
    - Large ketonuria
    - Weight loss (5% of pre pregnancy weight)
  - Electrolyte, thyroid, and hepatic abnormalities may also be present but not diagnostic

Pathogenesis of HG

- **Remains largely unknown**
- **Psychological factors**
  - Conversion/Somatization disorder
  - Response to stress
- **Endocrine**
  - Elevated HCG
  - Estrogen
- **Gastrointestinal**
  - Abnormal GI motility

Risk Factors for HG

- **Multiple gestation**
- **Fetal anomalies**
  - Triploidy
  - Down syndrome
  - Hydrops fetalis-late
- **Gestational trophoblastic disease**
- **History**
  - Family
  - Previous Pregnancies

Maternal Effects

- **Wernicke's encephalopathy**
- **Central pontine myelinolysis**
- **Mallory Weiss tear**
- **Splenic avulsion**
- **Esophageal rupture**
- **Pneumothorax**
- **Peripheral neuropathy**
  - B6 and B12 deficiency

Fetal Effects of HG

- **Meta-analysis**

- **Outcomes**
  - Low birthweight
  - Small for gestational age
  - Preterm birth

Fetal Effects of HG

	Weight Loss	No Weight Loss
MBW	3064	3558
Percentile	38.1	72.0
>4000 gm	0 (0%)	6 (18%)
<10%	9 (32%)	2 (6%)

Gross et al., AJOG, 1989

Fetal Effects of HG

- **Population based retrospective cohort**
- **1,270 patients admitted with HG**
  - No difference in outcomes with pregnancy weight gain of 15.4 lbs or more
  - Low pregnancy weight gain (<15.4 lbs)
    - Low birth weight
    - Small for gestational age
    - Preterm delivery
    - 5 minute Apgar score <7

Dodds et al., Obstet Gynecol, 2006

Diagnosis of HG

- **Clinical diagnosis without uniform criteria**
- **Common criteria**
  - Weight loss greater than 5% of body weight
  - Ketonuria unrelated to other causes
  - +/- emesis > 3 times per day

NVP versus HG

- **Nausea and Vomiting in Pregnancy**
  - Normal vital signs and have normal physical and laboratory findings.
- **Hyperemesis Gravidarum**
  - Orthostatic hypotension, laboratory abnormalities, and physical signs of dehydration
  - May have ptyalism (excessive salivation)

Evaluation of HG

- **Remember that HG is a *Diagnosis of Exclusion***
- **Signs making HG less likely**
  - Abdominal pain
  - Fevers and chills
  - Abnormal neurological examination
  - Enlarged thyroid

Differential Diagnosis

- **Gastrointestinal**
  - Gastroenteritis, biliary tract disease, hepatitis, obstruction, PUD, pancreatitis, appendicitis
- **Genitourinary**
  - Infection, uremia, torsion, stones
- **Metabolic**
  - DKA, porphyria, Addisons, hyperthyroidism
- **Neurologic**
  - Pseudotumor cerebrii, vestibular lesions, migraine, tumors
- **Misc**
  - Psychological conditions, drug toxicities

Evaluation of HG

- **Vitals**
  - Weight
  - Orthostatic blood pressure and heart rate
- **Labs**
  - Serum electrolytes
  - Urine ketones and specific gravity
  - Other labs depending on circumstances
- **Ultrasound**

Other Labs Rarely Helpful

- **Liver function**
  - LFTs high in 50% of women with HG (< 300 mg/dL)
  - Bilirubin commonly high (< 4 mg/dL)
- **Pancreatic Enzymes**
  - 10-15% of patients with HG
  - Up to 5 fold increase in amylase and lipase
- **Thyroid function**
  - 70% of patients with HG have low TSH
  - Elevation in T4 and T3 common
- **Hemoconcentration**
  - Nearly All

Goals of Treatment

- ***Reduce*** **symptoms changes in diet, environment, and/or medication**
- **Correct complications of severe nausea and vomiting**
- **Minimize fetal effects of nausea and vomiting and medications used to treat symptoms**

Management

Non-pharmacological Treatment

- **Don’t forget the simple stuff**
- **Reassure patients that this is normal**
- **Avoid triggers**
- **Avoid fatty, spicy foods**
- **Frequent small feedings**
- **Crackers at bedside in AM**
- **Avoid empty stomach**

Management

Non-pharmacological Treatment

- **Protein predominant meals may reduce nausea**
  - Avoid heavy carbohydrate meals
  - Avoid high fat meals
- **Liquids do not exacerbate gastric motility issues as much as solids.**

Jednak et al., Am J Physiol 277, 1999

Management

Uncomplicated Nausea and Vomiting

- **Outpatient management**
- **Antiemetics**
- **Intermittent hydration as necessary**
- **Remember vitamins!**
  - Vitamin B6, either 25 or 30ug: improvement in nausea
  - Vitamin B12- 25ug: no antiemetic effect

Sahakian et al., Obstet Gynecol 78,1991

Vutyavanich et al., Am J Obstet Gynecol 173, 1995

Czeizel et al., Arch Gynecol Obstet 251, 1992

Management

Antiemetics

- **Antihistamines**
- **Combination drugs**
  - *Diclegis ®*
- **Phenothiazines**
- **Prokinetic agents**
- **Seratonin antagonists**
- **Corticosteroids**

Management

Antiemetics

- **Antihistamines**
  - Doxylamine (Unisom), Dimenhydrinate (Dramamine), Diphenhydramine (Benadryl)
  - Great for first line management
  - Pooled analysis of controlled trials demonstrated a significant reduction in pregnancy related nausea and vomiting
  - Safety well established
  - Drowsiness and constipation

Magee et al., AJOG, 2002

Management
Antiemetics

- ***Diclegis®***
  - Oral B6 and Doxylamine, 10 mg/10 mg tabs
  - Originally *Bendectin®,* removed from US market in 1983 by manufacturer
    - "Best studied human nonteratogen"
  - Available as Diclectin in Canada
  - Generic alternative
    - Pyridoxine (50 mg): ½ tablet TID
    - Unisom (25mg): 1 tablet QHS or ½ tablet AM/PM
  - *"Not studied for use in hyperemesis gravidarum"*

Management

Antiemetics

- **Phenothiazines**
  - Promethazine (Phenergan), Procholperazine (Compazine), Chlorpromazine (Thorazine)
  - Adverse effects: sedation, hypotension, dry mouth, extrapyramidal symptoms
  - Available as oral, buccal, IV, IM forms
  - Category C but safety well-established

Management

Antiemetics

- **Prokinetic Agents**
  - Metaclopromide (Reglan)
  - Increases upper GI motility, lower esophageal sphincter tone
  - Dopamine antagonist
  - Safety established
  - Dystonic reactions reported

Management

Antiemetics

- **Serotonergic Agents**
  - Ondansetron (Zofran), Dolasetron (Anzemet), Granisetron (Kytril)
    - available in PO or disintegrating tablets
  - Ondansetron found to be superior to doxylamine/pyridoxine in RCT
  - Has become 1st line in many areas

RECENT POSTS

- The Daily Journal Selects Lieff Cabraser Attorneys As Top 100 Lawyers in California
- Jonathan Selbin to Speak at ABA Conference on Class Actions
- Law360 Names Richard Heimann A Trial Ace
- Suit Charges Negligence by Medical Device Manufacturer Pentax Medical and Chicago-Area Hospital Led to Patient Contracting Fatal Superbug Infection from Contaminated Medical Scope

CATEGORIES

- Accidents & Safety Recalls (2)
- Antitrust (14)

Blog

Sarah London Discusses Zofran Anti-Nausea Medication Birth Defect Injury Lawsuits

By Lieff Cabraser of Lieff Cabraser Heimann & Bernstein, LLP posted in Prescription Drug Injuries on Monday, July 6, 2015.

Management

Safety of Ondansetron

- **Possible adverse fetal effects**
  - Swedish registry: increased risk of VSD (OR:1.62)
  - Danish registry: no increase
  - US registry: no significant increase
- **Prolongation of QT interval**
  - FDA warning (2012)
  - Medication interactions

Management
Antiemetics

- **Corticosteroids**
  - Methylprednisolone
  - 16 mg po x 3 days, then taper by 4 mg/day x 2 weeks
  - Initial studies promising
  - Yost et al., 2003 (n=110)
    - No difference in rate of rehospitalization compared with placebo

Safari et al., AJOG, 1998

Yost, Obstet Gynecol, 2003

Management

Alternative Therapies

- **Acupuncture- studies conflicting**
  - Sweden (n=33): placebo vs acupuncture-helped
  - England (n=55): traditional acupuncture vs sham-no difference
- **Acupressure**
  - Sea-Band, Bioband
  - 7 trials to date-conflicting results, absence of blinded testing, no effect seen in largest study

Management
Alternative Therapies

- **Ginger**
  - Randomized double-blind trials
  - Reduced nausea and episodes of vomiting in ginger groups compared with placebo groups
  - 250 mg ginger capsules QID
  - Again – for NVP, not necessarily HG

Vutyavanich et al., Obstet Gynecol, 2001

Management

Extreme Circumstances

- **IV hydration**
  - With 5% dextrose/lactated ringers
  - 75-125 cc/hour
  - Replace thiamine!!!
- **Enteral tube feedings**
  - Nasogastric or nasoduodenal
- **Total parenteral nutrition**
  - Last resort

Jednak et al., Am J Physiol 277, 1999

The Problem with PICC Lines

- **PICC-stands for Peripheral Inserted Central Catheter**
- **Popular because of easy of insertion and patient tolerance**
- **Secure access to the central circulation**
  - Infusion therapy
  - Nutritional support

The Problem with PICC lines

- **Infection**

  Local
  - Catheter colonization
  - Exit or insertion site infection
  - Phlebitis
  - Tunnel infection

  Systemic
  - Bloodstream infection
  - Suppurative thrombophlebitis
  - Distant complications
- **Thrombosis**

The Problem with PICC lines

- **Allen et al. JVIR, 2000**
  - Thrombosis in 38% of 344 lines
  - 40.7% in patients with solid tumors
- **Ogura et al. AJOG, 2003**
  - 52 pregnant patients
  - 26 of the patients (50%) had a complication (thrombosis, mechanical failure or infection)
- **AVOID PICC LINES AND PARENTERAL NUTRITION**

Treatment Algorithm

Initial therapy:

Vitamin B6 10-25 mg TID
Doxylamine 12.5 mg TID

Promethazine 12.5-25 mg q 4 hours PO/PR

Or

Dimenhydrinate 50-100 mg q 4-6 hours PO/PR

If no improvement

Treatment Algorithm

Dehydration?

No

Metoclopromide 5-10 mg q 8 hours IM/PO

Ondansetron 4-8 mg q 6 hours IM/PO

Prochlorperazine 5-10 mg q 3-4 hours IM/PO or 25 mg BID PR

Promethazine 12.5-25 mg q4 hr IM/PO/PR

Yes

IV Fluid Replacement

IV Multivitamin Replacement

IV Antiemetics

Metoclopromide 5-10mg q8 hr IV

Prochloperazine 2.5-10mg q3-4 hr IV

Promethazine 12.5-25mg IV q4 hr

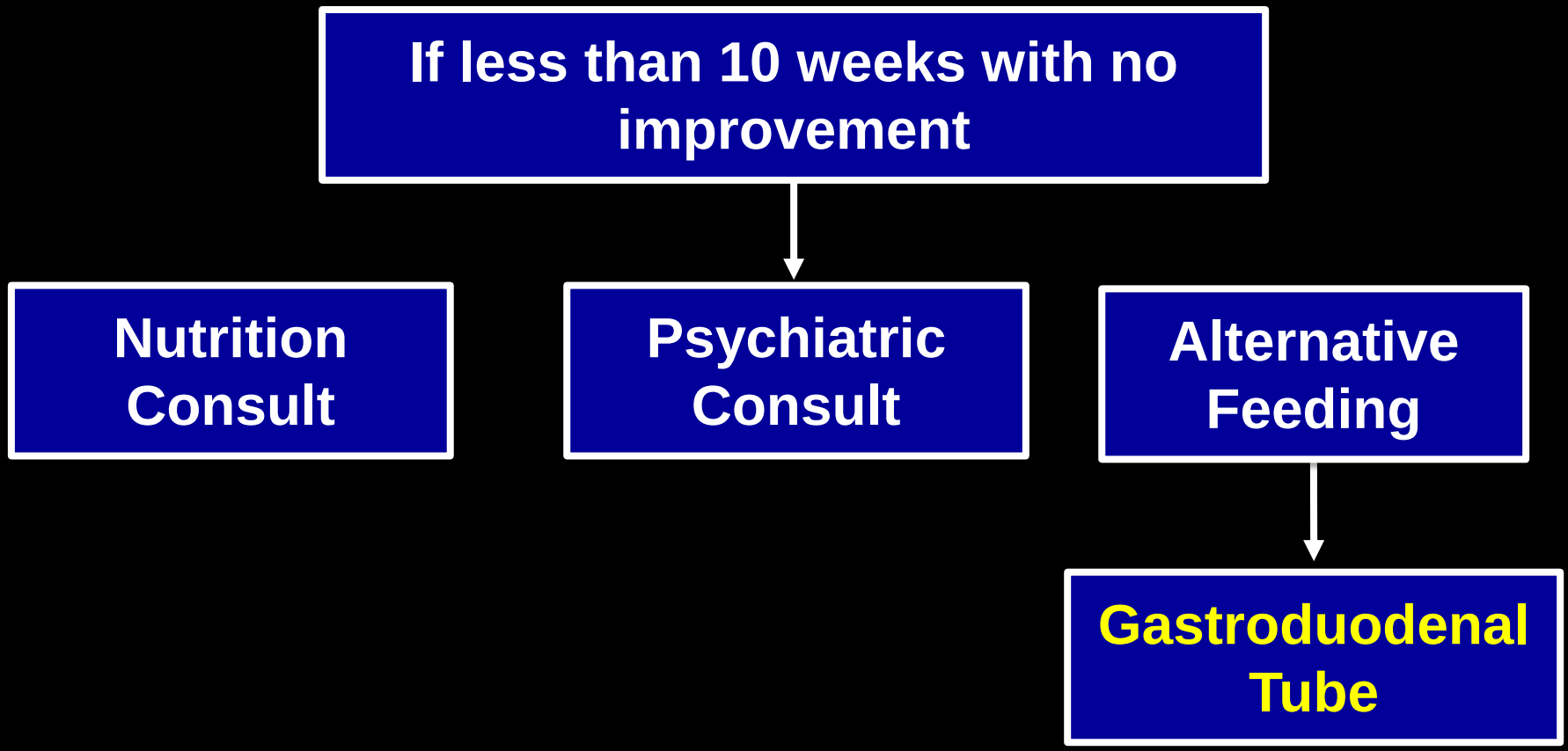
Ondansetron 4 mg IV q6 hr

If no improvement 

Treatment Algorithm

If over 10 weeks, consider addition of corticosteroids

Treatment Algorithm



Conclusion

- HG is a severe complication of pregnancy
- Don’t ignore nausea and vomiting
- Try to manage as outpatient with focus on organized, protocol based care
- With severe disease, admission to hospital is appropriate

Conclusion

- Inpatient management should focus on appropriate IV hydration, vitamin and antiemetic therapy with progress to outpatient management
- If no improvement, nutrition/psych consults
- Place a nasoduodenal tube (no TPN) if nutrition needed
- Avoid PICC lines if at all possible!

Wernicke's Encephalopathy

- **Classic Triad**
  - Ophthalmoplegia 37%
  - Gait Ataxia 28%
  - Confusion 18%
- **Rare-cases reported regularly**
- **Never give dextrose without thiamine first!!**
  - 100 mg thiamine IVP daily for 2-3 days
  - 3 mg oral or parenteral thiamine daily

Central Pontine Myeliolysis

- **Occurs with rapid correction of sodium in a hyponatremic patient**
- **Severe neurologic symptoms, often irreversible**
- **Plasma sodium concentration**
  - Only increase 10-12 meq/L in first day
  - Increase 18 meq/L in next two days

Utah Experience

- **Patients admitted with HG between 1998-2004**
  - Singleton viable intrauterine pregnancy documented by first trimester ultrasound
  - At least one 24 hour admission to the hospital for treatment of nausea/vomiting
  - The presence of laboratory abnormalities
  - Weight loss
- **Compared maternal and fetal outcomes**
- **Cases assigned to one of three groups**
  - Medication alone
  - PICC line
  - Nasogastric or Nasoduodenal tube

Utah Experience

- **Excluded patients if significant maternal gastrointestinal disease or had PICC line and NG/ND tube utilized**
- **94 patients met study criteria and had complete outcome data available**
  - 33 had a PICC line placed (35.1%)
  - 19 had a NG/ND placed (20.2%)
  - 42 had medication alone (44.7%)

Utah Experience

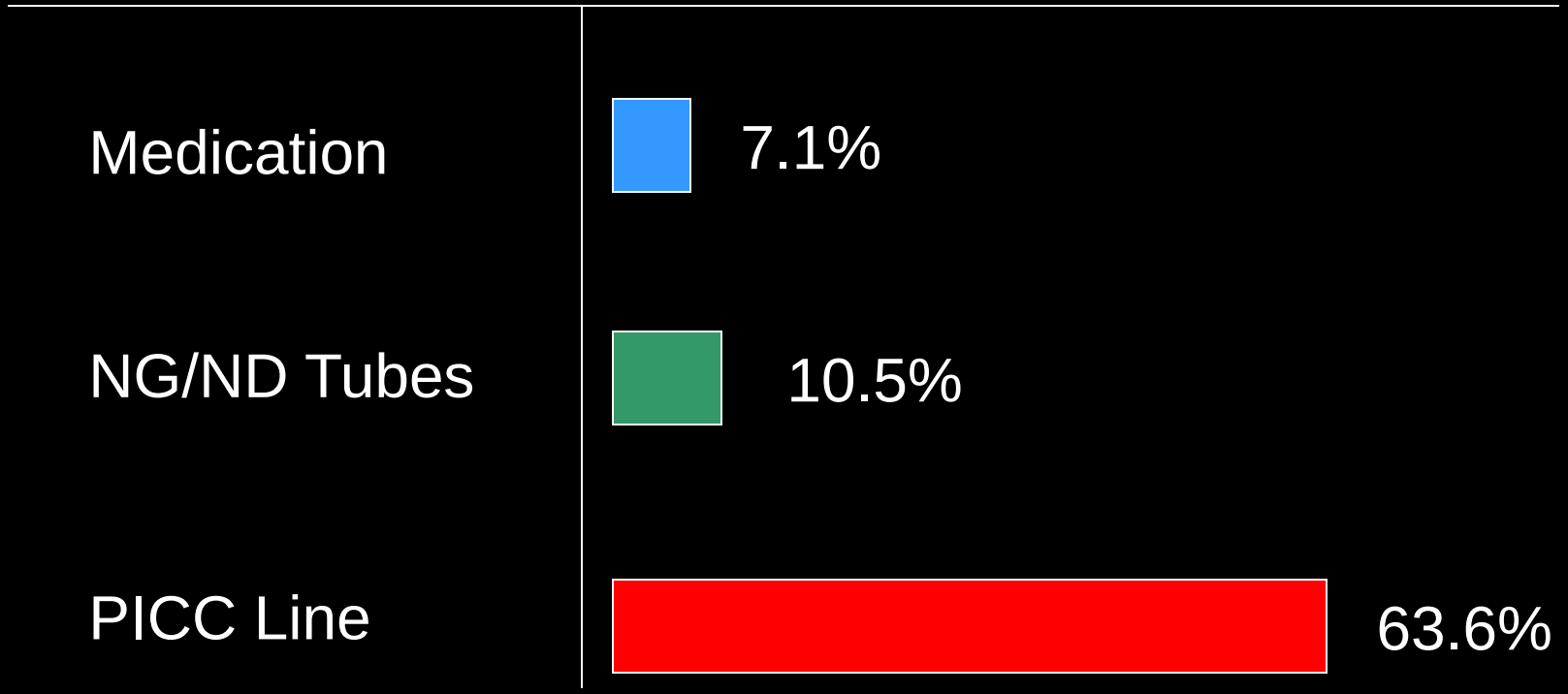
	PICC Line	NG Tube	Medication Alone	P-value
Maternal Age	27.5 ± 5.16	26.1 ± 5.00	23.3 ± 5.56	0.21
Gravidity	2.18 ± 1.61	1.94 ± 0.97	1.75 ± 0.92	0.33
Maternal Weight Loss	12 ± 6.02	10 ± 10.4	8.0 ± 3.65	0.34
Gestational Age at Delivery	36.9 ± 2.99	37.5 ± 1.71	38.3 ± 2.02	0.07

Utah Experience

	PICC Line	NG Tube	Medication Alone	P-value
Fetal Weight at Delivery	2842 ± 680	3097 ± 418	3156 ± 488	0.07
1 Minute Apgar	7.76 ± 1.05	8.0 ± 1.19	7.46 ± 1.68	0.39
5 Minute Apgar	8.88 ± 0.44	8.88 ± 0.32	8.74 ± 0.55	0.41
SGA	6.1% (2/33)	0%	0%	NS
Admissions to NICU	9.1% (3/33)	0%	4.7% (2/42)	NS
Terminations	9.1% (3/33)	5.3% (1/19)	0%	NS
Fetal Loss	9.1% (3/33) 12,14,20 weeks	0%	2.4% (1/42) 10 weeks	NS

Utah Experience

Complications



Utah Experience

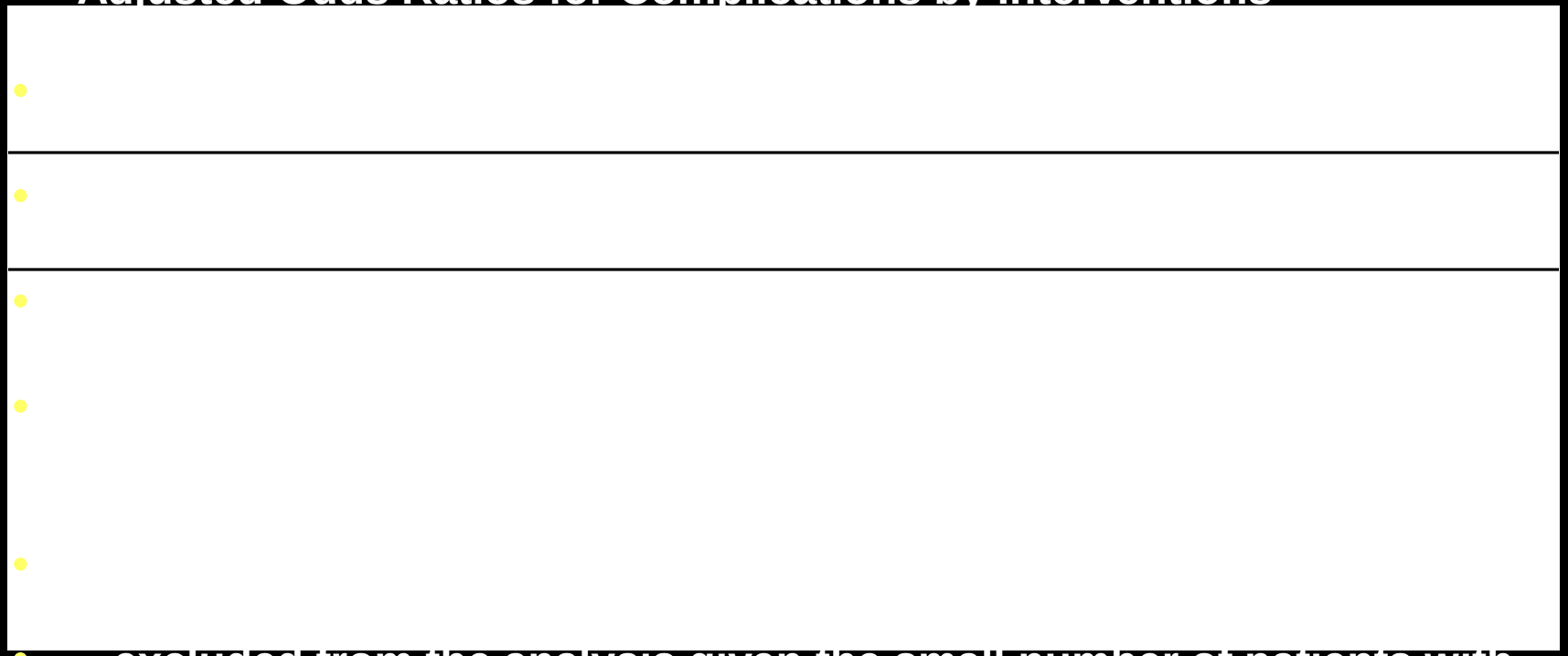
Treatment Strategy	Complications
Medication	3/42-Adverse reaction to medication
NG/ND	2/19-Displacement of tube
PICC Line	8/33-Thrombosis 5/33-Localized cellulitis 5/33-Bacteremia or sepsis 2/33-Thrombosis and infection 1/33-Pulmonary embolus

Utah Experience

- Ten patients had significant infection requiring intravenous antibiotics and/or removal of PICC line
- Eight patients with thrombosis requiring removal of the line and/or anticoagulation with heparin or LMWH
- Two patients had both
- Two patients required removal and replacement of the PICC line secondary to catheter occulsion
- One patient had a pulmonary embolus

Utah Experience

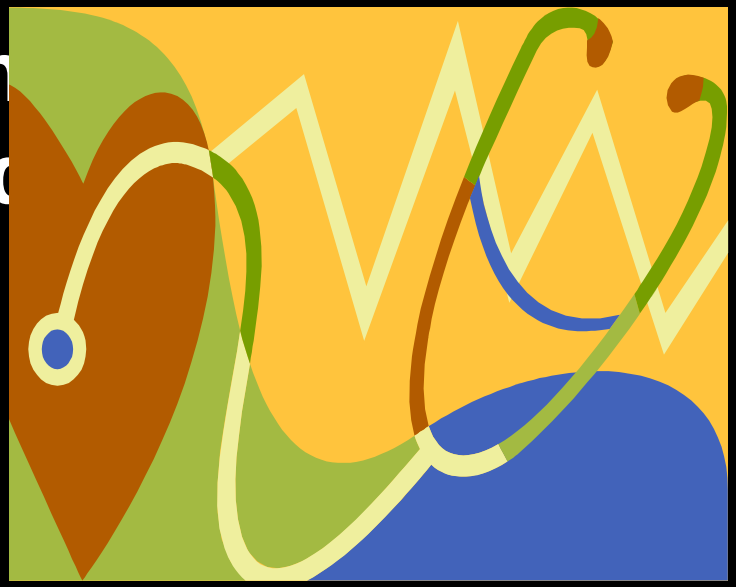
- Adjusted Odds Ratios for Complications by Interventions



- excluded from the analysis given the small number of patients with these conditions

Utah Experience

- Outside of this study, there was a report of infectious en requiring ICU care and replacement



Utah Experience

- **May need nutrition**
- **Get nutrition consult/Use nasoduodenal tube**
  - Hsu JJ et al., Obstet Gynecol, 1996
    - Review of hyperemesis patients revealed good outcomes after Dobhoff tube placement
  - Folk JJ et al., J Reprod Med, 2004
    - TPN group had a marked and significant increase in serious complications directly related to TPN use