Pharmacologic Treatment Options for Common GI Complaints in Pregnancy...

When the first line fails or is not available

Rajaa Chatila, MD
Associate Professor of medicine
Director, Medicine Residency Program
Gilbert and Rose-Marie Chaghoury School of Medicine
Lebanese American University
Outline

1. Review the treatment options of common GI disorders in pregnancy
   1. Nausea and hyperemesis
   2. GERD
   3. Cholestasis and pruritus
   4. Constipation
   5. Gastroenteritis

2. Discuss second-line or newer forms of treatment options
Which Medications are Safe During Pregnancy?

For 95% of medications approved in the past 10 years, the fetal risk was "undetermined."

Adam et al Am J of Med Genet 2011
Nausea and Vomiting in Pregnancy

- 50-90% of women experience some extent of nausea early pregnancy
  - 91% of women experience it in first trimester
  - Drug treatment often coincides with the period during which the fetus is most susceptible to teratogenic effects.

- Hyperemesis gravidarum
  - Intractable vomiting associated with weight loss of more than 5% of pre-pregnancy weight, dehydration, electrolyte imbalances, ketosis
  - Need hospital admission
  - Receive intravenous rehydration and parenteral antiemetic drugs to avoid serious maternal and fetal morbidity

Severity of symptoms dictate type of management

**Mild forms:**
- Smaller or frequent meals
- More carbohydrates
- Less fat
- Antihistamines

**Severe Forms**

**Antiemetics**

**Safe Antiemetics**
- Meclizine [class B] or promethazine [class C]
  - Fetal adverse events have not been reported
  - Not recommended for routine use in pregnancy
- Metoclopramide [class B]
  - Crosses the placenta and produces substantial fetal blood alcohol effects
- Ondansetron [class B]

**Unsafe & Harmful Antiemetics**
- Prochlorperazine [class C]
- Diphenhydramine [class C]
- Trimethobenzamide

**Alternative Therapies**
- Pyridoxine (vitamin B-6) [class A]
- Corticosteroids [class C]
Once Vitamin B 6, hydration and antihistamines fail → antiemetics:
- Phenothiazine (Prochlorperazine, promethazine etc.)
- Dopamine antagonists (metoclopramide)
- Selective 5-hydroxytryptamine receptor antagonists (Ondansetron)

In intractable vomiting:
- Consider parenteral antiemetics or combination of antiemetics

In cases of severe, resistant, hyperemesis gravidarum:
- Consider corticosteroids

Metoclopramide (Primperan):

- Prokinetic agent, a dopamine antagonist.
  - FDA: black-box warning:
    - Rare cases with tardive dyskinesia
    - Risk of this complication a function of duration of treatment and the total cumulative dose
    - Avoid treatment for more than 12 weeks
Nausea and Vomiting In Pregnancy

Ondansetron

- A cohort compared 176 exposed to 352 non-exposed to Ondansetron:
  - no significant differences in pregnancy and fetal outcomes

- A case–control study:
  - Increased risk of cleft palate but not of cleft lip, hypospadias, or neural-tube defects

- In a cohort, Pasternak studied the association of Ondansetron use with risk of adverse fetal outcome:
  - No increase in the risk of spontaneous abortion, stillbirth, any major birth defect, preterm delivery, or infants born with low birth weight or born small for gestational age.
  - No cases of cleft palate among 1233 infants exposed in the first trimester
  - Study not powered to assess the risks of individual defects
  - Study cannot definitively rule out the possibility of adverse effects by ondansetron, but does provide reassurance

# Antiemetic Doses and FDA Pregnancy Risk Category

Phenothiazines, Dopamine agonists and 5HT3 Receptor antagonists

<table>
<thead>
<tr>
<th>Phenothiazines</th>
<th>Extrapyramidal symptoms, sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promethazine (Phenergan)</td>
<td>25 mg every 4–6 hr</td>
</tr>
<tr>
<td></td>
<td>C  Severe tissue injuries with intravenous use (black-box warning); oral, rectal, or intramuscular administration preferred</td>
</tr>
<tr>
<td>Prochlorperazine (Compazine)</td>
<td>5–10 mg every 6 hr</td>
</tr>
<tr>
<td></td>
<td>C  Also available as buccal tablet</td>
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<table>
<thead>
<tr>
<th>Dopamine antagonists</th>
<th>Sedation, anticholinergic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethobenzamide (Tigan)</td>
<td>300 mg every 6–8 hr</td>
</tr>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Metoclopramide (Reglan)</td>
<td>10 mg every 6 hr</td>
</tr>
<tr>
<td></td>
<td>C  Tardive dyskinesia (black-box warning)</td>
</tr>
<tr>
<td>Droperidol (Inapsine)</td>
<td>1.25 mg to 2.5 mg intramuscularly or intravenously only</td>
</tr>
<tr>
<td></td>
<td>C  Black-box warning regarding torsades de pointes</td>
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</table>

<table>
<thead>
<tr>
<th>5-hydroxytryptamine3-receptor antagonist</th>
<th>Constipation, diarrhea, headache, fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron (Zofran)</td>
<td>B  Also available as oral disintegrating tablet; more costly than oral ondansetron tablets</td>
</tr>
</tbody>
</table>
Corticosteroids

- Seems more effective than standard antiemetics, at reducing hospital admissions, but may be associated with adverse effects.

- Glucocorticoid Risks:
  - Cleft lip with or without cleft palate
    - 3-4 times increased risk when steroids are used before 10 weeks of gestation: the higher the doses the greater risks.

  ➔ glucocorticoids to be used only after 10 weeks of gestation
Corticosteroids for Refractory Cases

If steroids are needed because of failure to respond to conventional treatment options include:

- **Hydrocortisone**, followed by prednisolone:
  - Intravenous hydrocortisone 100 mg, twice daily
  - When better, oral prednisolone 40-50 mg daily to be gradually tapered until the lowest maintenance dose that controls symptoms is reached.

- **Methylprednisolone**:
  - 16 mg every 8 hr for 3 days, then taper over 2 weeks
  - Maximum duration of therapy 6 weeks to limit serious maternal side effects

Itopride (Ganaton)

- Increases the release of acetylcholine (ACh) through dopamine D2-receptor antagonistic action and inhibits decomposing released ACh through its acetylcholine esterase (AChE) inhibitory action→ gastrointestinal motility.

Enhancement of the Gastrointestinal Motility

- **Activation of the gastric motility**
  - activates the gastric motility dose-dependently in conscious dogs.

- **Activation of the gastric emptying ability**
  - Itopride hydrochloride activates gastric emptying ability in humans, dogs and rats.
Other Promotility agents

Itopride (Ganaton)

- Safety in pregnancy and lactation not established
  - Excreted in breast milk in the animal experiments (rats)

- Only when expected therapeutic benefits outweigh the possible risks associated with treatment may it be used
Other Promotility agents

Mosapride (Mosar)

- Pregnancy Category C
  - Adverse effect on the fetus in animals
  - No adequate and well controlled studies in humans but potential benefits may warrant use of the drug in pregnant women despite potential risks
GERD in Pregnancy

- Treatment via a Step-up approach:
  - 1st line
    - Antacids
    - Alginates
  - 2nd line
    - H2 receptor blockers
    - Promotility agents (metoclopramide)
  - 3rd line
    - Proton pump inhibitors

Proton Pump Inhibitors

- Most PPIs FDA category B
  - Data from Pasternak et al., prospective cohort study ²
    (Studied PPI exposure before and during pregnancy and the risk of major birth defects)
    - Exposure within 4 weeks before pregnancy was associated with major birth defects
    - Possible limitations- patients had reflux pathology prior to pregnancy & other possible comorbidities

- In general:
  - PPIs pose a low risk to cause birth defects,
  - Should not be a reason to terminate pregnancy
  - Recommended to delay PPI therapy till after 1st trimester

1. Drugs 2012; 72 (2): 171-179
<table>
<thead>
<tr>
<th>3rd line Proton-pump Inhibitors</th>
<th>FDA Category</th>
<th>Observations from: Drugs 2012; 72 (2): 171-179</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Omeprazole</strong></td>
<td>C*</td>
<td>• Embryotoxic and fetotoxic in animals. Case reports in human suggest similar concerns.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• * The most clinical experience in humans being the first available PPI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• According to the Swedish Medicines Information Engine, FASS – it is considered category A (well controlled epidemiological studies indicating no adverse effects on pregnancy and or fetus.</td>
</tr>
<tr>
<td><strong>Esomeprazole</strong></td>
<td>B</td>
<td>• No fetal teratogenicity or harm. Limited human pregnancy date</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Exposure during the first 4 weeks prior to pregnancy and during the 1st trimester was associated with a non-significant increase in birth defects</td>
</tr>
<tr>
<td><strong>Lansoprazole</strong></td>
<td>B</td>
<td>• No fetal teratogenicity or harm. Limited human pregnancy date</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Significant increase in birth defects when used prior to pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Non-significant increase in defects when used during the 1st trimester</td>
</tr>
<tr>
<td></td>
<td></td>
<td>⇒ Due to possible risks, despite the study limitations, Lansoprazole is not considered first line</td>
</tr>
<tr>
<td><strong>Dexlansoprazole</strong></td>
<td>B</td>
<td>• Structurally similar to lansoprazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>⇒ Not considered first line</td>
</tr>
<tr>
<td><strong>Rabeprazole</strong></td>
<td>B</td>
<td>• No fetal teratogenicity or harm. Limited human pregnancy data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fewest data of all PPIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>⇒ Rabeprazole is not first line</td>
</tr>
<tr>
<td><strong>Pantoprazole</strong></td>
<td>B</td>
<td>• No fetal teratogenicity or harm. Limited human pregnancy data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No difference in birth defects but we have limited clinical experience</td>
</tr>
</tbody>
</table>
Lexicomp 2013:

- **Sodium Bicarbonate**: Should not be used in pregnancy
  - potential to cause metabolic alkalosis and fluid overload

- **Pregnancy Risk Factor: C**
  - Animal reproduction studies have not been conducted.

Cholestasis of Pregnancy

- Patient with pruritus usually referred to the gastroenterologist having already been to a dermatologist.

- A disorder of bile transport that has genetic and environmental etiologies.

- Troublesome pruritus of the third trimester but which may start much earlier as well.

- Serious implications on fetal well-being including: fetal distress; unexplained stillbirth, meconium staining and fetal asphyxia.
CHOLESTASIS of PREGNANCY

- Cochrane review (2013)
  - Included 21 trials with a total of 1197 women
  - They were mostly at moderate to high risk of bias.

- Danxiaoling and Yiganling (Chinese herbal medicines)
  - Danxiaoling significantly better improvement in pruritus in comparison to Yiganling.
  - DXL Normalized liver enzymes and bile salts and decreased cholesterol level
UDCA

- Pruritus
  - Superior to placebo in five (228 women) out of seven trials

- Preterm Births
  - Significantly fewer with UDCA (RR 0.46; 95% CI 0.28 to 0.73; two trials, 179 women)

- Fetal Distress
  - No significant difference (RR 0.99; 95% CI 0.41 to 2.36, two trials, 109 women).

- UDCA compared to dexamethasone (83 women), showed a significant improvement with UDCA in a subgroup of women with severe obstetric cholestasis.
S-Adenosyl methionine (SAMe)

- **S-adenosyl L-methionine (SAMe)**
  - Improves estrogen-induced impairment of bile flow and membrane alterations in animal experiments. Results in humans, however, are conflicting.

  - Conflicting evidence in pruritus control
  - SAMe less effective than Urso for pruritus (four trials; 133 women)
  - Using combination of Urso with SAMe is of no added benefit (conflicting data)
Superiority of UDCA
- SAMe (four trials; 133 women)
- Cholestyramine (one trial; 84 women)
- Dexamethasone (83 women) in severe cholestasis

SAMe alone superior to placebo (two trials; 68 women)

Combination UDCA with SAMe not more effective than UDCA alone (1 trial 16 women)

- Insufficient evidence for the efficacy in cholestasis of pregnancy (alone or in combination)
  - SAMe, guar gum, activated charcoal, dexamethasone, cholestyramine, Salvia, Yinchenghao decoction (YCHD), Danxioling and Yiganling, or Yiganling

CHOLESTASIS of PREGNANCY

- Ursodeoxycholic acid (UDCA) Pregnancy category B
  - UDCA 14–16 mg /kg p.o. qd, divided in two to three daily doses, over 3 weeks leads to improvement of symptoms and laboratory chemistries.
  - High-dose UDCA (1.5–2.0 g p.o./day) reduces abnormal maternal and fetal bile acid levels


H. Dancygier, Clinical Hepatology, 1257 DOI: 10.1007/978-3-642-04519-6_98, © Springer-Verlag Berlin Heidelberg 2010
Cholestasis in Pregnancy

## Therapy For Cholestasis

### Cholestyramine (category C)
- Oral *cholestyramine (8 g/day)*, (BID or TID dosing)\(^1\)\(^2\)
- Prolonged intake results in malabsorption of fat soluble vitamins
- Vitamin K should be administered 10 mg i.m. qw to avoid fetal bleeding.

### Antihistamines (category B/C)
- NOT effective. Moreover, they impair the reaction capacity and increase fatigue. \(^2\)

### Steroids (category: C)
- Exhibit a beneficial effect in isolated cases and may promote fetal lung maturity.

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2. H. Dancygier, Clinical Hepatology, 1257 DOI: 10.1007/978-3-642-04519-6_98, © Springer-Verlag Berlin Heidelberg 2010
Other Therapeutic Options

- **Opioid antagonists (naloxone, naltrexone)** - *Pregnancy category C*
  - Highly beneficial in many studies
  - Prevent the binding of endogenous opioid agonists, which are elevated in cholestasis.

- **Ondansetron:** *Pregnancy category B*
  - Based on the possible implication of the serotonin neurotransmitter system in the pathogenesis of pruritus in cholestasis
  - Little data supports the use of ondansetron as therapy.


Pregnancy risk categories extracted from Lexicomp 2013.
Rifampicin, Pregnancy category C

- A semi-synthetic antibiotic.
- Rifampicin and phenobarbital act as rapid and strong inducers of the enzymes of the microsomal drug-oxidizing system, promoting the metabolism of endogenous ‘pruritogenic’ compounds.
- Rifampicin competes for the uptake of Bile Salts into the hepatocyte, eliminating their detergent effect.
- Rifampicin (antimicrobial action), modifies the synthesis of secondary Bile Acids in the intestinal lumen, and consequently reduces the amount of hepatotoxic lithocholic acid.

Pregnancy risk categories extracted from Lexicomp 2013
Constipation

- Incidence 11-38%
- Etiology multifactorial
  - Decreased small bowel motility
  - Decreased motilin level
  - Decreased colonic motility
  - Increased absorption of water
  - Iron supplementation
Constipation in Pregnancy

**Therapy**

- **Probably Safe:**
  - Fiber supplements
    - Rarely effective
    - Worsens bloating
  - Stool softeners & Osmotic Laxatives
    - sodium docusate; lactulose; PEG
  - Stimulant laxatives
    - for intermittent use but should not be used regularly

- **To be avoided:**
  - Castor oil and mineral oil
Mechanism of Action

- Linaclotide and its active metabolite bind and agonize guanylate cyclase-C on the luminal surface of intestinal epithelium.
- cGMP intracellular and extracellular concentrations lead to chloride and bicarbonate secretion into the intestinal lumen.
- Intestinal fluid increases and transit time is decreased.
- Extracellular cGMP may decrease visceral pain by reducing pain-sensing nerve activity.

No data/experience in pregnancy yet
Linaclotide

Current approved indications:
- Chronic idiopathic constipation (CIC): Oral: 145 mcg once daily
- Irritable bowel syndrome with constipation (IBS-C): Oral: 290 mcg once daily

Pregnancy Risk Factor C
- Pregnancy Considerations
  - Adverse events were observed in some animal reproduction studies.
  - Linaclotide and its metabolite are not measurable in plasma when used at recommended doses.
Antimicrobials in Pregnancy

- Most antimicrobials cross the placental barrier
- Few solid data on the teratogenic potential of most antimicrobial agents in humans
- Experience suggests that certain drugs are unlikely teratogenic and are safe for pregnant women:

<table>
<thead>
<tr>
<th>Safe, non-teratogenic</th>
<th>Category D</th>
<th>Unsafe, teratogenic potential (category X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Tetracyclines</td>
<td>Quinine</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
<td>Ribavirin</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>Miltefosin</td>
</tr>
<tr>
<td>INH, rifampicin, ethambutol</td>
<td></td>
<td>Quinolones</td>
</tr>
</tbody>
</table>
Gastroenteritis in Pregnancy

Metronidazole

FDA Labeling; Contraindication in 1st trimester¹, but CDC recommends using in any stage of pregnancy if needed².

- No teratogenic effects observed in animal reproduction studies.

- Few reports of facial anomalies after in utero exposure, most studies have not found an increased risk of congenital abnormalities following maternal use of metronidazole during the first trimester of pregnancy.

- In studies that included women during all trimesters of pregnancy, an increased risk of adverse fetal and neonatal outcomes was not observed.

- Use of oral metronidazole is contraindicated during the first trimester (per the FDA approved labeling)

1. Package insert PFIZER LAB-0162-6.2. Revised June 2013
3. LEXICOMP 2013
Ciprofloxacin

- Adverse events have been observed in some animal reproduction studies.
- An increased risk of teratogenic effects has **not** been observed in animals or humans following ciprofloxacin use during pregnancy.
- **Concerns of cartilage damage in immature animals** ➔ ciprofloxacin should only be used during pregnancy if a safer option is not available.
Bismuth subsalicylate (Peptobismol, Pink Bismuth)

- Bismuth absorption negligible but the salicylate is almost 80% absorbed
  - Category D in third trimester
Dioctahedral smectite (Smecta)

- A non-absorbable type of clay
- Chelates toxins in the gut and binds to the mucus layer making it thicker
- May be used for acute gastroenteritis (viral or bacterial)
- Safe in pregnancy
- <1% side effects (constipation), and <0.001% allergic reaction)
Physico-chemical characteristics of Diosmectite

- **Diosmectite**
  - A natural silicate of aluminium and magnesium
  - A powder, the particles of which are tiny (+ 1µ)
  - Each particle consists of a pile of lamellae or leaves

Stacked layers

Layer structure

1 of 3 µ

Silica
Alumina
Silica

1 nm
Because of its physicochemical characteristics, Diosmectite has a:
- High adsorption capacity
- Potent coating capacity

The key physicochemical properties are:
- The tiny size of the particles
- Their formation into sheets
- Their layer structure

Staphylococcus haemolytic toxin
Staphylococcus cytotoxic toxin
Strychnine
Escherichia coli toxin
In conclusion

› Avoid drugs if you can afford to without compromising maternal health

› Always try to avoid medications in the first trimester the period of embryogenesis

› Do not forget that fetus continues to develop throughout and drugs may harm bones and cartilage forming or precipitate infection or bleeding when used in 2nd and 3rd trimesters

› Consult a clinical pharmacist to help you out in choosing the safest drug when needed