Medication use Before and During Pregnancy

April 13, 2013

Millie D. Long MD, MPH

Outline

• Review of pregnancy
  – Medication safety grading system
  – Normal fetal development
  – Birth outcomes in general population

• Endoscopy in the pregnant patient
  – Monitoring, positioning
  – Medication safety

• Epidemiology, fertility, and medication use during pregnancy in selected GI disorders
  – GERD
  – IBD
Background: GI diseases and pregnancy

- Chronic GI and liver diseases affect women during the reproductive years
- Endoscopic evaluation can be needed during pregnancy to diagnose or treat gastrointestinal illness
- Medications used as therapies for chronic diseases can affect fertility
- Medications also vary in regards to safety during pregnancy and breastfeeding

Background: Medication Safety

- Current FDA grading system has been in place since 1975: Includes categories A-X
  - A: no risk in adequate, well-controlled studies in humans (<1%)
  - B: no risk in animal studies; no well controlled human studies during pregnancy
  - C: risks in animal studies; no well controlled human studies during pregnancy; benefits may outweigh risks (66%)
  - D: risk in human studies; benefits may outweigh risks
  - X: animal or human studies demonstrate fetal abnormalities; risks outweigh benefits; contraindicated
Background: Medication Safety

• FDA has recently begun to revamp this system, the letter classifications will be removed and a structured narrative for both pregnancy and lactation will be provided including:
  – Risk summary
  – Clinical considerations
  – Data
• For now, pregnancy categories A-X are still referenced

Fetal Development

• 1st trimester: organ development
  – Week 3: the brain, spinal cord and heart begin to develop and the GI tract starts to form.
  – Weeks 4 and 5: limb development, further brain development. Eyes and ears, regular heart beat.
  – Week 7: all the major organs have begun to form.
• 2nd trimester: further maturing of the organs
  – Respiratory system has developed by week 25 such that gas exchange is possible.
• 3rd trimester: continued development with rapid growth of the gravid uterus.
Birth Outcomes General Population

- Early Pregnancy Loss 15% - 24%
- Prematurity 8-10% of all pregnancies
- Birth Defects 2 – 4% of pregnancies

National Center for Health Statistics, 2009 data

Endoscopy

- Each year in the US, among pregnant women there are:
  - Over 12,000 with a strong indication for EGD
  - Over 6,000 with a strong indication for colon/sig
  - Over 1,000 with a strong indication for ERCP.
- If the benefit outweighs the risk to the fetus, endoscopy should be performed.
- Optimal time is in the 2nd trimester, after organogenesis and prior to the later months where trauma and stimulation of the enlarging uterus are possible

Risks to consider with endoscopy

- Teratogenicity of the drugs used during endoscopy (including bowel preparations)
- Medication (sedation) induced hypoxia and hypotension
- Induction of pre-mature labor and fetal trauma.


Monitoring and positioning

- Monitoring
  - Pre-viable: fetal heart tones are assessed at the beginning and the end of the procedure.
  - Viable: consider continuous fetal monitoring along with monitoring for uterine contractions (in consultation with OB)

- Positioning
  - The enlarging gravid uterus can compress the aorta and the vena cava if the patient is in the supine position, resulting in decreased blood flow to the placenta.
  - Use the left lateral decubitus position.

Endoscopy Medication use

• Sigmoidoscopy bowel preparation
  – Tap water enema

• Colonoscopy bowel preparation
  – Polyethylene glycol (PEG) electrolyte solutions (C) are considered the safest option
  – Magnesium citrate may cause electrolyte disturbances in selected patients
  – Hyperphosphatemia and renal failure has been described with the use of sodium-phosphate based products


Endoscopy Medication use

• Acceptable sedation medications (B/C)
  – Meperidine (B)
    • Several large studies with no teratogenicity in 1st trimester
    • Not recommended with breastfeeding
  – Fentanyl (C)
    • No teratogenicity in humans, use low dose
    • Compatible with breastfeeding
  – Propofol (B)
    • Considered low risk
    • Peak levels in breast milk at 4 hours, pump/discard at 4 hours

• Avoid class (D) medications
  – Benzodiazepines (D)
    • Cross the placenta, potential for neonatal respiratory depression
    • Pump/discard milk 4 hours after use
Advanced Endoscopy Techniques

- Electrocautery
  - Amniotic fluid conducts electrical current
  - Bipolar current when needed

- ERCP
  - When indicated, use no or limited fluoroscopy
  - Radiation shielding of fetus
  - Position left lateral decubitus

- PEG
  - Ultrasound to identify dome of uterus
  - Pelvic wedge to avoid compression of vena cava


GERD: Epidemiology and Pathophysiology

- Heartburn occurs in 80% of women during pregnancy
- Can occur in any trimester
- Increases with gestational age
- Atypical symptoms are common (cough, chest pain, globus)
- Lower esophageal sphincter pressures are lower during pregnancy due to hormonal changes
- Increased intra-abdominal pressure from enlarging, gravid uterus

Therapy for GERD in Pregnancy

• 1st line: lifestyle changes (can resolve symptoms in up to 25% of patients)
  – Avoidance of ETOH, tobacco
  – Limit heartburn and reflux inducing foods
    • Chocolate
    • Peppermint
    • Citrus
  – Eat small, frequent, low fat meals
  – Chewing gum between meals to stimulate salivary secretions (reduce esophageal acid exposure)
  – Elevate head of bed
  – Avoid eating within 3 hours of bedtime


GERD: Medications and Pregnancy

<table>
<thead>
<tr>
<th>H2 blockers</th>
<th>FDA Pregnancy Category</th>
<th>Pregnancy Comment</th>
<th>Breastfeeding Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famotidine</td>
<td>B</td>
<td>Paucity of safety data</td>
<td>Limited human data: probably compatible</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>B</td>
<td>Low risk</td>
<td>Limited human data: probably compatible</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PPI</th>
<th>FDA Pregnancy Category</th>
<th>Pregnancy Comment</th>
<th>Breastfeeding Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole</td>
<td>B</td>
<td>Limited data: low risk</td>
<td>No human data: potential toxicity</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>B</td>
<td>Limited data: low risk</td>
<td>No human data: potential toxicity</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>C</td>
<td>Embryonic and fetal toxicity reported, but large data sets suggest low risk</td>
<td>Limited human data: potential toxicity</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>B</td>
<td>Limited data: low risk</td>
<td>No human data: potential toxicity</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>B</td>
<td>Limited data: low risk</td>
<td>No human data: potential toxicity</td>
</tr>
</tbody>
</table>

GERD: Medications and Pregnancy

- In a meta-analysis of 2398 H2 blocker exposed subjects, no increased odds of congenital malformations
- In a meta-analysis of 1530 PPI-exposed pregnancies, no significant increased rate of congenital malformations with PPI.

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Log (adjusted OR) (SE)</th>
<th>Adjusted OR (random) 95% CI</th>
<th>Weight %</th>
<th>Adjusted OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson et al.</td>
<td>0.4283 (0.0039)</td>
<td>4.70 (1.55, 15.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kallio et al.</td>
<td>0.1570 (0.0053)</td>
<td>7.46 (1.71, 34.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lakh et al.</td>
<td>0.5085 (0.0793)</td>
<td>2.98 (1.71, 2.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pragada et al.</td>
<td>0.1976 (0.0703)</td>
<td>7.37 (0.86, 12.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOVETTI et al.</td>
<td>0.1603 (0.1049)</td>
<td>1.69 (0.60, 4.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorn et al.</td>
<td>-0.0716 (0.0401)</td>
<td>0.89 (0.49, 1.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malick et al.</td>
<td>0.1133 (0.1614)</td>
<td>6.05 (1.12, 5.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (66%, CI)</td>
<td></td>
<td></td>
<td>100%</td>
<td>1.12 (0.86, 1.46)</td>
</tr>
<tr>
<td>Test for heterogeneity: $\chi^2 = 1.03, df = 6, P = 0.89, P^2 = 9%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.64, P = 0.40$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


GERD: Medications and Pregnancy

Rate of congenital malformations among 840,968 live births, PPI exposure during conception or 1st trimester

- 3.4 for PPI
- 2.6 for No PPI

*Increased odds limited to those with exposure in 4 weeks pre-conception in subanalysis

GERD: Summary Recommendations

- Lifestyle modifications
- Antacid, H2 blocker and PPI appear safe during pregnancy
- For those with reflux on PPI prior to pregnancy and uncomplicated disease, minimize exposure in conception/1st trimester periods if at all possible due to limited data on congenital malformation risk
  - Change to H2 blocker or discontinue when possible

IBD: Fertility and Counseling

- Fertility rates in the absence of surgery are similar to general population for CD and UC
- Pelvic surgery/adhesions increase infertility rates (weighted infertility rate 3 x greater after TAC/IPAA)
- Risk to offspring is 2-13 x higher when a parent has IBD
- Absolute risk to offspring 5% with 1 parent with CD, 1.7% with 1 parent with UC and 35% with both parents

Fertility in IBD: Men

- Sperm abnormalities may lead to infertility
- Sulfasalazine bad for sperm
  - Mesalamine, balsalazide → all OK
- 6-MP, Azathioprine → sperm normal (despite earlier reports as to fetal risks)
- Methotrexate → temporary low sperm count in animals, no evidence in humans
  - Outcomes of pregnancies with paternal exposure to MTX are normal
- Infliximab may decrease sperm motility


IBD and Pregnancy

- IBD can be associated with preterm birth and low birth weight of infants
- IBD can be associated with complications at the time of labor
- IBD is associated with an increased rate of caesarean section delivery
- Active luminal IBD prior to pregnancy is associated with increased complications
- Ideally a woman should enter pregnancy in remission

Effects of Pregnancy on IBD

Crohn’s Disease

Ulcerative Colitis

IBD: Medications and Pregnancy

- Older recommendations included stopping thiopurines during pregnancy
  - No longer true, reassuring data from renal transplant and IBD populations as to safety
- Older recommendations for biologics (infliximab/adalimumab) include “stopping rules” with discontinuation of therapies at the beginning of 3rd trimester
  - Levels still detectable in children regardless of stop date (not linear correlation)
  - No detrimental effects on children (vaccine response, infection) with circulating levels at birth
  - Continue these medications throughout pregnancy

Miller, JR Soc Medicine 1986;79:221-225

Outcomes of 6MP/AZA Therapy

<table>
<thead>
<tr>
<th>6-MP use (n)</th>
<th>Stopped 84</th>
<th>Conception 61</th>
<th>Throughout 15</th>
<th>Prior to 6MP 165</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAB</td>
<td>19 (23%)</td>
<td>10 (16%)</td>
<td>1 (6%)</td>
<td>32 (19%)</td>
</tr>
<tr>
<td>Pre-term</td>
<td>4 (5%)</td>
<td>3 (5%)</td>
<td>4 (27%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>LBW</td>
<td>3 (4%)</td>
<td>2 (3%)</td>
<td>1 (7%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Congenital Abnormalities</td>
<td>3 (4%)</td>
<td>2 (3%)</td>
<td>1 (7%)</td>
<td>6 (4%)</td>
</tr>
</tbody>
</table>

RR = 0.85 95% CI 0.47-1.55, p = 0.59 for successful pregnancy outcome on 6mp

No increased risk of conception failures (defined as a spontaneous abortion), abortion secondary to a birth defect, major congenital malformations, neoplasia, or increased infections among male or female patients taking 6-MP compared with controls


Intrauterine exposure of standard 6MP/Aza dose

- 30 women, median 6-TGN decreased over time throughout pregnancy, while 6-MMP increased, without causing myelotoxicity or hepatotoxicity
- After delivery, both 6-TG and 6-MMP levels returned to preconception baseline levels.
- Fetal 6-TGN concentrations correlated positively with maternal 6-TGN levels (p<0.0001).
- No 6-MMP was detected in the newborns
- All infants had normal Apgar scores, but 60% had anemia at birth.
- No major congenital abnormalities

Outcomes of Women Exposed to Infliximab During Pregnancy

![Bar chart showing the proportion of patients with different outcomes.]

- General population
- Crohn’s disease
- Infliximab patients
- Infliximab patients with CD


Anti-TNF and Pregnancy

- 4 women on infliximab during pregnancy stopped IFX therapy at week 21, 26, 26 and 30.
- In 3 infants, therapeutic IFX levels were present in cord blood at levels of 5.5–13.7 μg/mL and were 2-3x higher than in mothers.
- During the 3- to 6-month follow-up of children:
  - Normal development
  - No increased infections or allergic reactions
  - Normal antibody titers after childhood vaccinations

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Anti-TNF and Pregnancy

- 30 women on anti-TNF (infliximab and adalimumab) followed during pregnancy
- 12 (71%) discontinued infliximab treatment before gestational week 30; all patients remained in remission.
- All the patients taking adalimumab discontinued treatment before gestational week 30; 2 patients had relapses of IBD.
- Outcomes of pregnancies: 28 live births, 1 miscarriage among patients taking infliximab (at gestational week 6), and 2 miscarriages among patients taking adalimumab (at weeks 6 and 8); no congenital malformations.


Levels in cord blood

- Mean cord blood level of infliximab was 6.4±1.6 μg/mL
  - Lower in women who received the drug ≤10 weeks before delivery (2.8±1.1 μg/mL) than in those who received infliximab closer to delivery (10±2.3 μg/mL; \( P=0.02 \)).
- Adalimumab was detected in 5 samples of cord blood (mean concentration, 1.7±0.4 μg/ml)
  - Only undetectable level from a woman who discontinued at week 22

### IBD: Medications and Pregnancy

#### 5-ASA

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Pregnancy Category</th>
<th>Pregnancy Comment</th>
<th>Breastfeeding Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>B</td>
<td>Low risk, replace folate daily</td>
<td>Probably compatible, possible diarrhea in infant</td>
</tr>
<tr>
<td>Mesalamine (Asacol, Asacol HD)</td>
<td>C</td>
<td>Low risk: possible skeletal and male reproductive abnormalities in animal studies (DBP), consider alternate 5-ASA</td>
<td>Probably compatible, DBP (dibutyl phthalate) in coating is excreted into breast milk, unknown effects</td>
</tr>
<tr>
<td>Mesalamine (all other brands)</td>
<td>B</td>
<td>Low risk</td>
<td>Probably compatible, possible diarrhea in infant</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>C</td>
<td>Low risk</td>
<td>Probably compatible, possible diarrhea in infant</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>B</td>
<td>Low risk</td>
<td>Probably compatible, possible diarrhea in infant</td>
</tr>
</tbody>
</table>

#### Immunomodulators

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Pregnancy Category</th>
<th>Pregnancy Comment</th>
<th>Breastfeeding Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MP/Azathioprine</td>
<td>D</td>
<td>Low risk, animal teratogen</td>
<td>Probably compatible, consider discarding breast milk produced in the 4 hours after dosing</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
<td>Contraindicated, teratogenic to humans</td>
<td>Contraindicated, immunosuppression</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>C</td>
<td>Low risk</td>
<td>Potential toxicity, immunosuppression</td>
</tr>
</tbody>
</table>

IBD: Medications and Pregnancy

<table>
<thead>
<tr>
<th>Biologic</th>
<th>FDA Pregnancy Category</th>
<th>Pregnancy Comment</th>
<th>Breastfeeding Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>B</td>
<td>Low risk, consider continuing</td>
<td>Probably compatible</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>B</td>
<td>Low risk, consider continuing</td>
<td>Probably compatible</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>B</td>
<td>Low risk, continue dosing through pregnancy</td>
<td>Probably compatible</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>C</td>
<td>Low risk</td>
<td>Probably compatible</td>
</tr>
</tbody>
</table>

Mode of delivery in IBD

• Mode of delivery at discretion of OB, except in case of active perianal disease and (perhaps) IPAA when caesarian section is indicated
  – Vaginal deliveries in patients with inactive perianal disease do not lead to exacerbation or progression of perianal disease
  – Vaginal delivery is low risk in IPAA, with return to pre-pregnancy function within 6 months.
    • If any concern about continence/sphincter, then c-section can be offered
**IBD Recommendations**

- Enter pregnancy in remission
- Continue medications during pregnancy (5ASA, thiopurine, biologics)
  - *Stopping rules for biologics no longer apply*
- Endoscopy OK when indicated, aim for 2\textsuperscript{nd} trimester, fetal monitoring and precautions apply
  - *Breastfeeding precautions for 4-24 hrs after sedation*
- Mode of delivery dictated by obstetric reasons
  - *C-section for perianal disease, possibly for J pouch*
- Breastfeeding
  - *OK on biologics*
  - *Likely OK on thiopurines, consider pumping and discarding 1\textsuperscript{st} bottle of breastmilk 4 hours after ingestion*


**Summary**

- No need to fear a pregnant patient with a chronic GI condition
- Treat the mother, what is best for her is best for fetus
  - *Scope when needed, best when done during the second trimester*
- Anti-reflux medications are generally safe during pregnancy
- We now have better data on medication safety and course of pregnancy in IBD
- Education and preconception counseling are important in IBD