Pregnancy and Fertility in the Patient with IBD

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Objectives

• Discuss the adverse pregnancy outcomes associated with IBD

• Identify which IBD medications are compatible for use during pregnancy and lactation

• Describe the recommendations that should be made to the multidisciplinary team involved in the care of the pregnant patient
Patient Profile

• 29 year old woman presents to office to discuss family planning

• Moderate to severe UC diagnosed 5 years ago
  – Therapy with mesalamine, prednisone and azathioprine in the past with no benefit

• In remission on infliximab 5 mg/kg for the last 1 year
  – Remains on azathioprine 50 mg daily and 5ASA 2.4 g daily

• She is very concerned about the safety of her medications in pregnancy and wants to stop them all
  – She is concerned about flare and wants to discuss colectomy as a way to get off medication prior to conception

• What do you tell her?
Fertility in UC Before and After IPAA

## Pregnancy Outcomes: Population Based Studies

### Cases Included

<table>
<thead>
<tr>
<th></th>
<th>IBD</th>
<th>UC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Birth</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LBW</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>SGA</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Congenital Malformation</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Caesarean Section</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Despite most pts having inactive/mild disease, increased risk of AE’s compared to the gen pop.

Mahadevan U et al. *Gastroenterology.* 2007;133:1106-1112
## Increase in Preterm Birth with Moderate to High Disease Activity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Crude Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW</td>
<td>1.1</td>
<td>0.3-4.0</td>
</tr>
<tr>
<td>LBW at term</td>
<td>0.9</td>
<td>0.1-8.5</td>
</tr>
<tr>
<td><strong>Preterm birth</strong></td>
<td><strong>3.4</strong></td>
<td><strong>1.1-10.6</strong></td>
</tr>
<tr>
<td>Congenital Anomalies</td>
<td>0.4</td>
<td>0.0-3.9</td>
</tr>
</tbody>
</table>

Danish population based study: Pregnancies with disease activity at any time (n=71) were compared to pregnancies without any disease activity (n=86)

Fertility and Disease Activity

• Women with IBD have similar rates of conception to non-IBD women unless they have surgery
  – IPAA would not help her pregnancy chances

• Once pregnant, even with inactive disease, there is an increased risk of complications
  – Moderate to severe disease may make this worse

• Being in remission on low risk medication is the best option for a healthy pregnancy

• What medications are low risk?
Aminosalicylates (B, C)

- Meta-analysis of 7 studies of 5-ASA drugs in pregnant patients with IBD: 5-ASA (n=642) vs. No medication (n=1158)

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital abnormalities</td>
<td>1.16</td>
<td>0.76-1.77</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>2.38</td>
<td>0.65-8.72</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>1.14</td>
<td>0.65-2.01</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>1.35</td>
<td>0.85-2.13</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>0.93</td>
<td>0.46-1.85</td>
</tr>
</tbody>
</table>

- Sulfasalazine (B) given w/ folic acid 1 mg BID
- Placental and breast transfer occurs
  - Potential allergic reaction newborn: watery diarrhea
- SAS not associated with kernicterus or displacement of bilirubin from albumin
- Olsalazine: Pregnancy category C
- Asacol: Pregnancy category C (DBP in coating)

Corticosteroids (C)

• Case-control study in 1st trimester
  – Increased risk of oral clefts
  – Overall risk of malformations low
  – In transplant setting:
    • Adrenal suppression in newborn
    • Premature rupture of membranes

• Compatible with breast feeding

• Budesonide (Entocort)
  – Orally inhaled budesonide not associated with increase risk of fetal abnormalities
  – 8 CD patients treated with oral budesonide (1)

Antibiotics

• Metronidazole (B) / Ciprofloxacin (C)
  – Low risk of teratogenicity
    • Metronidazole: prospective controlled study, 2 meta-analysis
      – However, 2nd, 3rd T use, 1st T cleft lip, palate
    • Ciprofloxacin: prospective controlled study low risk of defects
      – Affinity for bones, arthropathy in children
  – Breast feeding not advised on MNZL, probably compatible with ciprofloxacin
  – Minimal benefit in CD and UC with longer use-avoid

• Rifaximin: Pregnancy C
  – teratogenicity in animal studies
  – Safety in humans in pregnancy/breastfeeding unknown

• Amoxicillin/Clavulanic Acid: Pregnancy B
Azathioprine and Teratogenicity

- 189 pregnant women on AZA who contacted 1 of 7 teratogen information services compared to 230 pregnant women who took non-teratogenic treatments

<table>
<thead>
<tr>
<th></th>
<th>AZA</th>
<th>No AZA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of major malformations</td>
<td>3.5%</td>
<td>3.0%</td>
<td>.775 (OR 1.17; 95% CI 0.37-3.69)</td>
</tr>
<tr>
<td>Birth weight</td>
<td>2995</td>
<td>3252</td>
<td>.001</td>
</tr>
<tr>
<td>Gestational age</td>
<td>37.8</td>
<td>39.1</td>
<td>.001</td>
</tr>
<tr>
<td>Premature birth</td>
<td>21.4%</td>
<td>5.2%</td>
<td>.001</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>23%</td>
<td>6.0%</td>
<td>.001</td>
</tr>
</tbody>
</table>

Azathioprine/6MP

• Cesame: French cohort
  - 86 pregnancies (AZA), 84 (other drugs), 45 (no drugs)
  - Miscarriage: 36%, 33%, 40%
  - Congenital abnormalities: 3.6%, 7.1%, 0%
  - No significant differences were found between the three groups in overall pregnancy outcome.

• Swedish Medical Birth Register
  - 476 women used AZA in early pregnancy
  - Most common indication was IBD (>300)
  - Rate of CA 6.2% AZA vs. 4.7% other
    • OR 1.41, 95% CI: 0.98-2.04
  - Increased rate of VSD/ASD
    • OR 3.18, 95% CI: 1.45-6.04
  - Increased rate of preterm, LBW, SGA
    • Likely disease effect

Coelho: *Gut*. 2011 Feb;60(2):198-203
Breast Feeding While Taking AZA/6MP

• 8 lactating women received Aza 75-200 QD
  – Milk and plasma at 30, 60 min and every hour x 5

• Variation in bioavailability reflected in wide range in milk and plasma first 3 hours

• Major excretion in breast milk within 4 hours of drug intake

• Worst case scenario: max concentration 0.0075 mg/kg
  – In most cases, will be <10% of maximum concentration

Christensen S et al. Aliment Pharmacol Ther. 2008:28, 1209-1213
## Medication Safety Summary

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Category</th>
<th>Comment</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5ASA Asacol, olsalazine</td>
<td>B C</td>
<td>Asacol: DBP</td>
<td>Compatible (rare diarrhea)</td>
</tr>
<tr>
<td>Corticosteroids Budesonide</td>
<td>C C</td>
<td>Low risk T1: Cleft palate</td>
<td>Compatible</td>
</tr>
<tr>
<td>Azathioprine/6MP</td>
<td>D</td>
<td>Low risk</td>
<td>Compatible: Ideally wait 4 hours after dose</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>
Antiangiogenic Therapies

Infliximab

Adalimumab

Certolizumab pegol

Monoclonal antibody

Chimeric

Human

Infliximab

Adalimumab

Certolizumab pegol

PEGylated humanized Fab’ fragment

$2 \times 20$ kDa PEG

Adapted from: Hanauer SB. Rev Gastroenterol Disord. 2004;4(Suppl. 3):S18-S24
Anti-TNF’s: Safety

• **Infliximab (B)**
  - Katz: 100 infants exposed, similar rate of live births, SAB’s
  - TREAT: 117 exposed vs. unexposed with similar rate of miscarriage (10 vs. 6.7%) and neonatal complications (6.9% vs. 10%)
  - Trivial amounts detected in breastmilk (n=1, Ben Horin)

• **Adalimumab (B)**
  - 137 women enrolled in a prospective study in pregnancy and an additional 89 adalimumab exposed pregnant women in a registry. No increase in birth defects
  - Trivial amounts detected in breastmilk (n=1, Ben Horin)

• **Certolizumab (B) data on file**
  - 16 pregnancies: 4 LB, 8 TAB, 1 SAB, 1 PTB, 2 unknown
  - Not detected in breastmilk (n=1)

• **Natalizumab (C): IgG4**
  - 143 pregnant patients exposed to natalizumab
  - No birth defects reported

Placental Transfer of IgG Ab

- INF and ADA are IgG1 antibodies
- Fc portion of IgG actively transported across placenta by specific neonatal FcR
- Highly efficient transfer in 3rd T leads to elevated levels of drug in newborn

\[ r^2 = 0.87, \ p < 0.04 \]

B: Fetal

Placental Transfer

- **Infliximab:**
  - Study of 10 mothers on IFX
  - In all cases, infant and cord IFX level were greater than mother. 6 months to clear

- **Adalimumab**
  - Study of 10 mothers on ADA
  - In all cases, infant and cord ADA level was greater than mother. Up to 4 months to clear
  - ¾ pts who stopped ADA 35 days prior to delivery had a flare

- **Certolizumab**
  - Study of 10 mothers
  - In all cases, infant and cord levels were less than 2 mcg/ml even if mom dosed the week of delivery

Mahadevan U *Gastroenterol* 2007;132:A-144; Mahadevan et al. *Gastro* vol 140 Is 5, suppl 1, P S-796 Mahadevan U *Gastroenterology* 2009;136:146
Timing of Biologics

- Debate: stop drug early or continue scheduled?
  - Last dose infliximab at week 32 weeks gestation
    - No real delay if patient gets next dose immediately after delivery (assume delivery around week 40 gestation)
  - Last dose adalimumab at week 34-36
    - Stopping earlier may lead to flares
    - If needed, can continue throughout on schedule
  - Continue certolizumab throughout pregnancy
  - If mom flares, treat her!
  - No live virus vaccine for first 6 months for infants exposed to IFX or ADA during pregnancy
  - Never switch drugs during pregnancy purely for placental transfer issues

Mahadevan U. *Am J Gastroenterol.* 2011 Feb;106(2):214-23
PIANO: Pregnancy in Inflammatory Bowel Disease And Neonatal Outcomes

• Patients classified by exposure into four groups of drugs taken b/w conception and delivery:
  – Unexposed: no immunomodulators/biologics
  – Group A: AZA/6MP
  – Group B: INF, ADA, CZP
  – Group AB: Combination therapy

• Preliminary: Overall minimal differences among Group A, B, AB & unexposed group, except:
  – Increased risk in Group AB:
    • Any complications: OR 2.60 (1.35-5.00)
    • Preterm birth: OR 3.42 (1.59-7.37)
  – No increase in infections or birth defects to date by medication exposure

Mahadevan Gastroenterology 2010;138:S-106
Advice to Interdisciplinary Team

• Obstetrician:
  – Most IBD medications are low risk in pregnancy (exception methotrexate) and can be continued during pregnancy and lactation
  – Mode of delivery is per OB discretion except with active perianal disease at the time of delivery and perhaps J Pouch

• Pediatrician
  – No live virus vaccines in the first 6 months if infant exposed to infliximab or adalimumab in utero
  – All other vaccines can be given on schedule
  – Monitor for infections
Outcome

• The patient decided to stop azathioprine given her obstetrician’s anxiety and the feeling that it was not adding much to her regimen at this point
  – This is debatable! Azathioprine can be continued during pregnancy

• Mesalamine was continued
  – Would you switch from Asacol to another 5ASA? No human data of adverse events, but if similar drug without DPB in coating…

• She continued infliximab and received her last dose at week 32 and then the day after delivery 8 weeks later
  – The infant had serum IFX levels checked 10 weeks after birth. They were undetectable so rotavirus vaccine given

• The mother breastfed and had no colitis-related complications