Treatment of IBD in the Pregnant Patient

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Question 1

• Which of the following drugs should NOT be **actively** transported across the placenta in the third trimester of pregnancy
  1. Infliximab
  2. Adalimumab
  3. Certolizumab
  4. Natalizumab
Question 2

Which of the following drugs is COMPATIBLE with breastfeeding

1. Infliximab
2. Azathioprine
3. Sulfasalazine
4. All of the above
5. None of the above
Question 3

• All of the following are CATEGORY B risk in pregnancy, EXCEPT:
  1. Infliximab
  2. Adalimumab
  3. Certolizumab
  4. Natalizumab
  5. Mesalamine
Effect of Pregnancy on CD: Disease Activity at Conception

Disease activity during pregnancy in women with IBD

**Exposure:** IBD disease activity during conception, each trimester and the postpartum period (1 month)
- Inactive, mild, moderate, severe

Disease activity in Crohn’s disease
- Concept, T1, T2, T3, PP

Disease activity in ulcerative colitis
- Concept, T1, T2, T3, PP

### Pregnancy Outcomes: Population Based Studies

<table>
<thead>
<tr>
<th></th>
<th>IBD</th>
<th>UC</th>
<th>CD</th>
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</thead>
<tbody>
<tr>
<td>Preterm Birth</td>
<td>X</td>
<td>X</td>
<td>X X</td>
</tr>
<tr>
<td>Low Birth Wt</td>
<td>X</td>
<td></td>
<td>X X</td>
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<tr>
<td>Small Gest Age</td>
<td></td>
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<td>X</td>
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<tr>
<td>Caesarean Section</td>
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</table>

1. N = 756 IBD
2. N = 510 CD
3. N = 1531 UC
4. N = 107 UC, 155 CD

IPAA: Cumulative Incidence of Pregnancy Within 5 Years

Pregnancy-Risk Categories

A: Controlled human studies do not show risk to fetus; chance of risk remote
B: No evidence of risk to fetus in human studies; chance of risk remote but possible
C: Inadequate studies in humans; risk cannot be ruled out, but benefits may outweigh risks
D: Positive evidence of fetal risk; benefits might outweigh risks in life-threatening situations when safer drugs are ineffective
X: Contraindicated in pregnancy

# Safety of IBD Medications During Pregnancy

<table>
<thead>
<tr>
<th>Category B</th>
<th>Category C</th>
<th>Category D</th>
<th>Category X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide</td>
<td>Ciprofloxacin</td>
<td>Azathioprine†</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Cyclosporine</td>
<td>6-Mercaptopurine†</td>
<td>Thalidomide</td>
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<tr>
<td>Balsalazide</td>
<td>Diphenoxylate</td>
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<tr>
<td>Corticosteroids</td>
<td>Olsalazine</td>
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<tr>
<td>Sulfasalazine</td>
<td>Tacrolimus</td>
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<tr>
<td>Anti-TNF agents</td>
<td>Natalizumab</td>
<td></td>
<td></td>
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<tr>
<td>Metronidazole*</td>
<td>Corticosteroids</td>
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<td></td>
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<tr>
<td></td>
<td>Rifaximin</td>
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</tbody>
</table>

*Safe for use after first trimester. †Increasing use in pregnancy.


Aminosalicylates (B,C)

- Meta-analysis 7 studies: 642 5ASA vs 1158 no med
  - Congenital anomalies: OR 1.16 (0.76, 1.77)
  - Stillbirth OR 2.38 (0.65, 8.72)
  - SAB OR 1.14 (0.65, 2.01)
  - Preterm delivery 1.35 (0.85, 2.13)
  - LBW OR 0.93 (0.46, 1.85)
- Sulfasalazine given w/ folic acid 1 mg BID
  - Folic acid: neural tube defects, CV, GU, cleft palate
  - Case reports of congenital malformation
- 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. All others, B

Rahimi Reprod Toxicol 2008
• Case-control study in 1\textsuperscript{st} 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
• Entocort (budesonide)
  – Orally inhaled budesonide not associated with increase risk of fetal abnormalities
  – 8 CD patients treated with oral budesonide (Binion)
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 metronidazole, 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
Human Studies: 6MP/AZA (D)

- Transplantation Experience
  - Frequency of Congenital Abnormality in renal tx
    0.0-11.8% in 27 clinical series
  - No recurrent pattern of anomalies seen
  - No increase in anomalies (Armenti 1994) in kidney transplant
- No congenital anom in rheumatic ds, SLE
- Experience in IBD
  - Alstead (1990): 14 pts: 7 entire pregnancy: no CA
  - Francella (2003): Retrospective
    - 79F(24 UC), 76M(27 UC). 325 pregnancies
    - No difference in outcomes with 6mp exposure
    - Only 15 patients on 6mp throughout pregnancy
Azathioprine

- 189 pregnant women on AZA who contacted one of seven teratogen information services were compared to a cohort of 230 pregnant women who took non-teratogenic treatments.

- **Rate of major malformations did not differ** with six neonates each:
  - AZA (3.5%) vs control (3.0%) ($P = 0.775$; OR 1.17; CI: 0.37, 3.69).

So...although 6MP/AZA listed as category D.....

....the evidence suggests minimal to no increase risk in pregnancy.
Biologic Therapy in IBD

Infliximab (B)
Adalimumab (B)
Certolizumab (B)
Natalizumab (C)
Outcomes of Women Exposed to Infliximab During Pregnancy

- **General population**: 67% live births, 17% miscarriages, 16% therapeutic termination
- **Crohn’s disease**: 66% live births, 17% miscarriages, 11% therapeutic termination
- **All infliximab patients (N = 96)**: 67% live births, 15% miscarriages, 19% therapeutic termination
- **Infliximab patients with CD (N = 82)**: 67% live births, 13% miscarriages, 20% therapeutic termination

**References**
Infliximab in Pregnancy

10 Crohn’s disease patients intentionally exposed to infliximab during pregnancy

8 women received maintenance infusions
2 women received initial infusions

10 Live Births

- Congenital malformations (N=0)
- IUGR (N=0)
- SGA (N=0)
- Preterm (N=3)
- LBW (N=1)

8 Caesarean sections: 2 active luminal, 3 perianal disease, 1 preterm

## Infliximab in Cord Blood

<table>
<thead>
<tr>
<th>Pt #</th>
<th>1</th>
<th>2</th>
<th>3*</th>
<th>4*</th>
<th>5*</th>
<th>6</th>
<th>7*</th>
<th>8*</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Breastfed</td>
<td>15.1</td>
<td>1.4</td>
<td>19.2</td>
<td>3.8</td>
<td>4.8</td>
<td>14.5</td>
<td>16.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Mother INF (mcg/ml)</td>
<td>--</td>
<td>2.0</td>
<td>26.5</td>
<td>3.3</td>
<td>8.8</td>
<td>20.5</td>
<td>26.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Cord Blood INF at Birth</td>
<td>25.3</td>
<td>2.9</td>
<td>23.6</td>
<td>4.2</td>
<td>8.7</td>
<td>28.2</td>
<td>27.5</td>
<td>10.6</td>
</tr>
<tr>
<td>Newborn INF at Birth</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>--</td>
</tr>
</tbody>
</table>
High Serum Infliximab Levels in Newborn of a Mother Treated During Pregnancy

<table>
<thead>
<tr>
<th>Time (weeks) from birth</th>
<th>Breast fed 7 wks</th>
<th>Breast feed resumed Wk 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
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<td>4</td>
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<tr>
<td>10</td>
<td></td>
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<tr>
<td>13</td>
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Infliximab infusions (10 mg/kg)

- Birth 41 wks

<table>
<thead>
<tr>
<th>Infliximab level</th>
<th>µg/mL</th>
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<tbody>
<tr>
<td>Mother serum</td>
<td>40</td>
</tr>
<tr>
<td>Baby serum</td>
<td>40</td>
</tr>
<tr>
<td>Breast milk</td>
<td>0</td>
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Immune studies at 6 months:
- T and B lymphocytes normal
- IgG, IgM and IgA levels normal

Adalimumab (B)

- Organization for Teratology Information Specialists reports 27 women enrolled in a prospective study of adalimumab in pregnancy and an additional 47 adalimumab exposed pregnant women in a registry.

- The rate of spontaneous abortion, stillbirth, congenital malformation and preterm delivery was similar to the diseased comparison and the general population.

Certolizumab (B) Natalizumab (C)

- Certolizumab: data on file
  - Pegylated – *should not cross placenta*
  - 16 pregnancies:
    - 4 healthy infants, 8 IAB, 1 SAB, 1 preterm, 2 unknown

- Natalizumab (C):
  - IgG4, placental transfer in third trimester
  - 143 pregnant patients exposed to tysabri
  - No birth defects reported
# Safety of IBD Medications in Breast-Feeding

<table>
<thead>
<tr>
<th>Low Risk to Use When Warranted</th>
<th>Limited Data Available</th>
<th>Contraindicated</th>
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<tr>
<td>Oral mesalamine</td>
<td>Tacrolimus</td>
<td>Methotrexate</td>
</tr>
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<td>Topical mesalamine</td>
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<td>Cyclosporine</td>
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<td>Metronidazole</td>
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<td>Adalimumab</td>
<td>Ciprofloxacin?</td>
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<td>6-MP/AZA*</td>
<td></td>
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<tr>
<td>Infliximab</td>
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(*new evidence suggests safe)

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  3. Certolizumab
  4. **Natalizumab – category C**
  5. Mesalamine
Summary

• Disease control at conception improves pregnancy outcomes
• anti-TNF therapies are safe and thiopurines are probably safe during pregnancy
• Infliximab and adalimumab do cross the placenta in the third trimester. Preliminary evidence suggests that certolizumab does not cross
• Most IBD medications can be continued during breastfeeding
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