Women’s Health Issues in IBD

Maria T. Abreu, MD
Professor of Medicine
Chief, Division of Gastroenterology

Thank you Uma

Uma Mahadevan MD
Professor of Medicine
Co-Medical Director
UCSF Center for Colitis and Crohn’s Disease
Introduction

- Many women with IBD are of childbearing age
  - Fertility is similar to age matched women without IBD (except IPAA)

- The risk of adverse pregnancy outcomes (SAB, SGA, PTB) and complications of labor and delivery are increased compared to the general population
  - Preterm birth is clearly associated with active disease (OR 3.4, 1.1-10.6)

- To achieve or maintain remission during pregnancy, it is recommended that most IBD medications are continued
  - The safety of continuing medications has been debated

- Significant placental transfer of infliximab and adalimumab has been documented with levels being present for up to 6 months from birth
  - Certolizumab has minimal transfer noted at birth
  - Impact of this is unknown

Fertility: ECCO consensus statement

- no evidence that UC or inactive CD affect fertility [EL3]
- active CD may reduce fertility so strive for remission [EL3]
- no evidence that medication affects fertility in females [EL4]
- in males sulphasalazine and MTX causes reversible oligospermia [EL3]

1 Mahadevan. Gastroenterology 2007;133:1106-12
2 Norgard. Am J Gastroenterol. Sep 2007;102(9)
3 Mahadevan Clin Gastroenterol Hepatol. 2013 Mar

doi:10.1093/ecco-jcc/jju006
Preconception care leads to less disease relapse during pregnancy

- Prospective study; 2008-2013
  - Females of reproductive age with IBD attending IBD Pregnancy Outpatient Clinic (POC)
  - Study group (n=149): preconception IBD POC counseling (30 minute consult)
  - Control group (n=105): patients attending IBD POC when already pregnant

### Results:

<table>
<thead>
<tr>
<th></th>
<th>Control group (105)</th>
<th>Study group (149)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate intake</td>
<td>46</td>
<td>87</td>
<td>0.0001</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>1</td>
<td>19</td>
<td>0.0001</td>
</tr>
<tr>
<td>Discontinuation of IBD meds due to concerns of side effects</td>
<td>8</td>
<td>0</td>
<td>0.0033</td>
</tr>
<tr>
<td>Periconceptual disease activity</td>
<td>16</td>
<td>12</td>
<td>0.68</td>
</tr>
<tr>
<td>Disease activity during pregnancy</td>
<td>34</td>
<td>20</td>
<td>0.04</td>
</tr>
</tbody>
</table>


Preparation for Pregnancy

- Review medications and optimize
  - Stop Methotrexate, Asacol HD
- Confirm patient is in remission
  - Fecal Calprotectin
  - Colonoscopy

- Health Care Maintenance
  - Surveillance colonoscopy, pap smear, etc
  - Vaccinations
  - Laboratory markers: Vitamin D, Iron studies, etc
Increase in Preterm birth with moderate to high disease activity

<table>
<thead>
<tr>
<th></th>
<th>Crude Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW LBW at term</td>
<td>1.1</td>
<td>0.3-4.0</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>3.4</td>
<td>1.1-10.6</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) 


IBD and Pregnancy: Overlapping Pathways

- Animal models: During pregnancy, shift Th1:Th2 balance by placenta which produces Th2 cytokines (IL4) and progesterone
- Maybe why UC patients seem to have more disease activity than Crohns patients in pregnancy?

Nasef. Translational Research 2012;160:65-83
Management of Flares

- **Medication choices are similar**
  - Avoid new aza/6mp in pregnancy
  - Avoid metronidazole, steroids in T1

- **Laboratory/Stool Tests**
  - Liver enzymes (Alk Phos), ESR may be elevated
  - Albumin may be low; mild anemia normal
  - C. difficile,
  - Calprotectin

- **Imaging**
  - MRI preferred to CT, though no gadolinium in T1
  - Ultrasound!

- **Endoscopy:** Unsedated flexible sigmoidoscopy

- **Surgery:** Indications similar to non-pregnant patient; T2 best time

Method of Delivery

- **Delivery should be at the discretion of the obstetrician**
- **Most women with IBD can have an uncomplicated vaginal delivery**
- **Exceptions:**
  - Women with active perianal disease should have a cesarean section. Women with inactive perianal disease may deliver vaginally without increased complications1
  - Women with an ileoanal J pouch should consider cesarean section, though vaginal delivery is possible2
- **Preserve sphincter function and continence later in life**

C-section (CS) and Risk of IBD?

- CS delivery disturbs the normal bacterial colonization of the newborn's intestine.
- Swedish Case-Control study 1536 cases:
  - CS increased risk of pediatric CD among boys (OR = 1.25, 95% CI 1.01-1.54) but not girls, (OR = 0.99, 95% CI 0.76-1.29)
- Danish Population Based study:
  - 32.6 million person-years of follow-up
  - CS increased risk of IBD at age 0-14 years (IRR 1.29, 95% CI 1.11-1.49)
  - Assuming causality, an estimated 3.2% of IBD cases before age 15 years were attributable to cesarean section
- Henderson: increase in IBD risk restricted nearly all to boys
  - IRR=1.26 (1.15,1.37) vs. 1.06 (1.15 among girls)
  - Higher for UC than CD


FDA Pregnancy Category

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>5ASA</td>
<td>B</td>
</tr>
<tr>
<td>Asacol, olsalazine</td>
<td>C</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>C</td>
</tr>
<tr>
<td>Budesonide</td>
<td>C</td>
</tr>
<tr>
<td>Azathioprine/6MP</td>
<td>D</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>B</td>
</tr>
</tbody>
</table>

Maria T. Abreu, MD

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Asacol Related Birth Defects

Dibutyl Phthalate is in the coating of Asacol and Asacol HD tablets

<table>
<thead>
<tr>
<th></th>
<th>Asacol</th>
<th>Non-Asacol SASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>117</td>
<td>156</td>
</tr>
<tr>
<td>M:F</td>
<td>60:56</td>
<td>77:73</td>
</tr>
<tr>
<td>Congenital Anomalies</td>
<td>7 (6%)</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>Urogenital Defects</td>
<td>2 M (3.3%)</td>
<td>2 M (2.5%)</td>
</tr>
<tr>
<td></td>
<td>1 F</td>
<td></td>
</tr>
</tbody>
</table>

- The OR 1.32 [CI: 0.18-9.63] for urogenital defects in male offspring
- After adjusting for disease type, age, smoking, history of surgery, anti-TNF use, and azathioprine/6MP use separately and in a multivariate model, the odds ratio did not change

A. Singh, Mahadevan DDW 2013

PIANO: Pregnancy Outcomes Amongst Mothers With IBD Exposed to Systemic Corticosteroids (CS)

Outcomes Significantly Associated with Corticosteroid Exposure During Pregnancy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth</td>
<td>1.8 (1.0-3.1)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>2.8 (1.3-6.1)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>2.8 (1.3-6.0)</td>
</tr>
</tbody>
</table>

Outcomes Not Significantly Associated with Corticosteroid Exposure During Pregnancy

<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformations</td>
</tr>
<tr>
<td>• Analyzed as any corticosteroid exposure vs unexposed and 1st-trimester exposed vs 1st-trimester unexposed</td>
</tr>
<tr>
<td>• Cleft palate reported in non-steroid group only</td>
</tr>
<tr>
<td>Developmental delay</td>
</tr>
</tbody>
</table>

Thiopurines and congenital malformations: Meta-analysis

Maternal

Thiopurines and fetal anemia: Should we test newborns?

- Fetal 6-TGN concentrations correlated positively with maternal 6-TGN levels (p<0.0001). (n=25)
  - Median 6TGN infant: mother = 42:92 pmol/8x108
- No 6-MMP was detected in the newborns except 1
  - Pancytopenia and high alk phos (severe pre-eclampsia)
- 63% had anemia at birth: (n=16)
  - Median Hb 9.25 mmol/l [8.25-9.60]
- 6-TGN 230 vs 90 in infants with anemia
- Congenital Anomalies: 2/31 (6.5%)
  - clubfoot, ptosis

Jharap B et al Gut 2013 Feb 19. (Epub ahead of print)
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


Structure of Common Anti-TNFs

- Infliximab (Remicade®)
- Etanercept (Enbrel®)
- Adalimumab (Humira®)
- Golimumab (Simponi®)
- Certolizumab pegol (Cimzia®)


Certolizumab pegol is structurally different: PEGylated, univalent, and does not have an Fc

Monoclonal antibody

Recombinant p75 TNF receptor/Fc fusion protein

All 4 reagents are bivalent and have an active isotype Fc
**Background**

**Human Placental Transfer**

- Active transport of IgG one way across the placenta by the neonatal FcRn receptor which binds to the CH2 and CH3 domain of the Fc
  - All 4 subclasses of IgG can pass to the foetus

- Preferential transfer of IgG1
  - 3rd trimester: IgG represents a major component of the umbilical venous blood with the majority of transfer occurring in the 3rd trimester

- IgG transferred via the placenta will persist longer in the newborn than the mother
  - Half-life of IgG in newborns is twice as long as the mother at 48.4 days

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### Level of IFX in Cord Blood and Newborns

<table>
<thead>
<tr>
<th>Pt No</th>
<th>Last dose (days)</th>
<th>Mother IFX μg/mL</th>
<th>Cord IFX μg/mL</th>
<th>% maternal levels</th>
<th>Baby IFX μg/mL</th>
<th>IFX undetected (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>15.1</td>
<td>-</td>
<td>-</td>
<td>25.3</td>
<td>168%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1.4</td>
<td>2.0</td>
<td>143%</td>
<td>2.9</td>
<td>207%</td>
</tr>
<tr>
<td>3#*</td>
<td>14</td>
<td>19.2</td>
<td>26.5</td>
<td>138%</td>
<td>23.6</td>
<td>123%</td>
</tr>
<tr>
<td>4*</td>
<td>90</td>
<td>3.8</td>
<td>8.8</td>
<td>183%</td>
<td>4.2</td>
<td>111%</td>
</tr>
<tr>
<td>5*</td>
<td>120</td>
<td>4.8</td>
<td>8.8</td>
<td>118%</td>
<td>8.7</td>
<td>118%</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>14.5</td>
<td>20.5</td>
<td>141%</td>
<td>28.2</td>
<td>194%</td>
</tr>
<tr>
<td>7*</td>
<td>46</td>
<td>16.5</td>
<td>26.5</td>
<td>164%</td>
<td>27.5</td>
<td>167%</td>
</tr>
<tr>
<td>8*</td>
<td>35</td>
<td>2.2</td>
<td>8.4</td>
<td>382%</td>
<td>10.6</td>
<td>482%</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>4.1</td>
<td>13.6</td>
<td>332%</td>
<td>4.7</td>
<td>115%</td>
</tr>
<tr>
<td>10</td>
<td>74</td>
<td>5.1</td>
<td>20.4</td>
<td>400%</td>
<td>8.4</td>
<td>165%</td>
</tr>
</tbody>
</table>

### Active Placental Transfer with ADA

<table>
<thead>
<tr>
<th>Time between last ADA dose and birth (days)</th>
<th>Maternal ADA level at birth μg/mL</th>
<th>Cord blood ADA level μg/mL</th>
<th>Infant ADA level at birth μg/mL</th>
<th>% maternal levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1**</td>
<td>7</td>
<td>6.25</td>
<td>9.72</td>
<td>156%</td>
</tr>
<tr>
<td>2*</td>
<td>56</td>
<td>1.84</td>
<td>5.72</td>
<td>311%</td>
</tr>
<tr>
<td>3**</td>
<td>7</td>
<td>3.94</td>
<td>4.65</td>
<td>118%</td>
</tr>
<tr>
<td>4*</td>
<td>42</td>
<td>0</td>
<td>0.158</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>2.2</td>
<td>4.32</td>
<td>196%</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>3.21</td>
<td>4.74</td>
<td>148%</td>
</tr>
<tr>
<td>7*</td>
<td>42</td>
<td>3.36</td>
<td>8.94</td>
<td>266%</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>16.1</td>
<td>19.7</td>
<td>122%</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>2.24</td>
<td>4.95</td>
<td>220%</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>8.48</td>
<td>8.29</td>
<td>98%</td>
</tr>
</tbody>
</table>

*LOQ 3.13 ng/ml  
*T3 flare; *post-partum flare
Concentrations of CZP Detected on Day of Birth

<table>
<thead>
<tr>
<th>Pt No</th>
<th>Last CZP dose prior to delivery (days)</th>
<th>Mother CZP μg/mL</th>
<th>Cord CZP μg/mL</th>
<th>% maternal levels</th>
<th>Baby CZP μg/mL</th>
<th>% maternal levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>18.8</td>
<td>1.7</td>
<td>8.8%</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>59.6</td>
<td>0.9</td>
<td>1.6%</td>
<td>1.0</td>
<td>1.7%</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>4.9</td>
<td>1.2</td>
<td>24.4%</td>
<td>1.2</td>
<td>25.1%</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>20.1</td>
<td>0.6</td>
<td>2.8%</td>
<td>0.4</td>
<td>2.2%</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>16.5</td>
<td>&lt;0.41</td>
<td>-</td>
<td>&lt;0.41</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>34.7</td>
<td>1.7</td>
<td>4.8%</td>
<td>1.6</td>
<td>4.5%</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>1.9</td>
<td>&lt;0.41</td>
<td>-</td>
<td>&lt;0.41</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>6.3</td>
<td>&lt;0.41</td>
<td>-</td>
<td>0.6</td>
<td>9.2%</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>42.7</td>
<td>1.3</td>
<td>3.0%</td>
<td>1.3</td>
<td>3.1%</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>37.8</td>
<td>0.6</td>
<td>1.5%</td>
<td>0.6</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Summary of placental transfer of biologics

- Infliximab levels in mothers, cord blood and newborns studied in 10 cases of patients with CD
- Adalimumab studied in 10 patients and showed the same results as infliximab
- CZP levels in 10 mothers, 12 cord blood and newborn samples measured using the validated ELISA
- Summary of drug measurements:

<table>
<thead>
<tr>
<th></th>
<th>IFX</th>
<th>ADA</th>
<th>CZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>11</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Day of birth drug level in infant, μg/ml range</td>
<td>2.9 – 39.5</td>
<td>4.28 – 17.7</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Median ratio cord: maternal drug level, % (range)</td>
<td>160 (87 – 400)</td>
<td>179 (98 – 293)</td>
<td>3.9 (1.5 – 24)</td>
</tr>
<tr>
<td>Length of time levels detectable</td>
<td>2 – 7 months</td>
<td>≥11 weeks</td>
<td>Not tested</td>
</tr>
</tbody>
</table>
Placental Transfer: Begins Early!

- 28 live births (17 IFX, 11 ADA)
  - Mean GA 39 [32-42]
  - Pts with active disease continued tx (5)
  - 10 pts on thiopurines, continued through pregnancy
- IFX: 12/17 d/c week 18-27
  - Mean cord level 6.4 + 1.6 µg/ml (2.8 vs. 10 p=0.02 if >10 weeks)
  - 14 restarted (week 8-27 postpartum)
  - 1 allergic rxn, 2 changed to ADA: 3/12 (25%)
- ADA: All 11 pts stopped week 22
  - Mean cord level 1.7 + 0.4 µg/ml
  - 2/11 relapsed – [18%] (CS wk 30; C section week 37)
  - all resumed therapy f/u 9 mos
- 22 % (5/23) had a flare or need to change therapy postpartum.
  - Account for preterm birth, continuing thiopurines, presence of detectable levels even when discontinued <30 weeks.

Zelinkova Clin Gastroenterol Hepatol. 2013 Mar

Infections

- Fatal case of disseminated BCG infection in an infant born to a mother on INF for Crohn’s disease
  - 10 mg/kg q 8 weeks monotherapy
  - Healthy boy delivered 36 wks. No Breastfeeding
  - BCG at 3 months, died at 4.5 months
  - Post-mortem: disseminated BCG
- 15 children vaccinated with BCG after TNF exposure without complications

Cheet K J of Crohn’s Colitis 2010
Bortlik Inflammd bowel dis 2014: 20:495-501
PIANO: Anti-TNFα Therapy in Third Trimester is Not Associated with Increased Adverse Outcomes

Outcomes Not Significantly Associated with Biologic Exposure During Pregnancy

- Preterm birth
- Disease activity in 3rd trimester or 4 months post-partum
- Infections out to 1 year of age
- Controlled for age, preterm birth, anti-TNFα use


PIANO: Achievement of Developmental Milestones Among Offspring of Women with IBD

In utero exposure to immunomodulator and biologic therapy did not lead to developmental delay compared to unexposed infants

Breastfeeding

- **Infliximab**
  - Breastmilk 1/200th mother’s level (n=1)¹
  - Peak concentrations in BM 100 ng/ml
  - Induction therapy: (n=1) infant levels 1700 ng/ml (maternal level 78,300 ng/ml)³

- **Adalimumab**
  - Breastmilk 1/200th mother’s level (n=1)²
  - ADA undetectable in infant serum (n=1)³

- **Certolizumab**
  - Not detected in breastmilk (n=1)


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Breastfeeding

- 75% of women reported breastfeeding
  - Unexposed women were more likely to BF (85%) than exposed (p<.0001)
    - 65% (A), 71% (B), 61% (AB)
  - Controlling for drug exposure, breastfeeding was **not associated with**:
    - Infection risk
    - Height and weight
Biologics in pregnancy

- Pregnant women with IBD are at increased risk for adverse events, but not based on biologic therapy
  - We continue biologics through T3
- Further studies are ongoing
  - Developmental milestones
  - Vaccine response
  - Correlation of placental levels and complications
  - T and B cell development

Management of IBD in Pregnancy

- Patient:
  - Education on medication safety and disease risk helps compliance
- Gastroenterologist:
  - Disease should be in remission
  - Medication optimized, health care maintenance updated
- 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 time of delivery and perhaps J Pouch
- Pediatrician
  - No live vaccines in the first 6 months if infant exposed to biologic (except certolizumab) in utero
  - All other vaccines can be given on schedule
  - Monitor for infections