Managing IBD in the Childbearing Years

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The University of Pennsylvania

Disclosures

- None
Overview

- Fertility
- Effect of IBD on Pregnancy
- Effect of Pregnancy on IBD
- Medication use in Pregnancy
- Mode of Delivery
- Medication use with Breastfeeding

Fertility in IBD
Fertility

- **Women**
  - Quiescent IBD & no history of pelvic surgery = same as general population
  - Active disease & pelvic surgery increase infertility

- **Men**
  - Nutrition
    - Zinc deficiency
  - Medications
    - Sulfasalazine
    - Methotrexate
    - Anti-TNFα

**References**


How will IBD affect pregnancy?
The pregnant IBD patient

- Women with IBD are at increased risk of pregnancy complications
- Active disease is a risk factor for adverse outcomes
  - Disease at conception
    - Spontaneous abortion, preterm birth
  - Flare during pregnancy
    - Preterm birth, still birth, low birth weight

**Table: IBD vs Control**

<table>
<thead>
<tr>
<th></th>
<th># studies</th>
<th>Pts w IBD(n)</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW</td>
<td>3</td>
<td>1033</td>
<td>2.10 (1.38 to 3.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Premature birth</td>
<td>8</td>
<td>1716</td>
<td>1.87 (1.52 to 2.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGA</td>
<td>4</td>
<td>1097</td>
<td>1.87 (0.61 to 5.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Still births</td>
<td>4</td>
<td>1243</td>
<td>1.48 (0.89 to 2.47)</td>
<td>0.13</td>
</tr>
<tr>
<td>Congenital</td>
<td>4</td>
<td>637</td>
<td>2.37 (1.47 to 3.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-section</td>
<td>6</td>
<td>1441</td>
<td>1.50 (1.26 to 1.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Nguyen et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy


<table>
<thead>
<tr>
<th></th>
<th>Pts w/o IBD n (%)</th>
<th>IBD patients n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-section</td>
<td>37 (9.5%)</td>
<td>61 (13.8%)</td>
<td>.05</td>
</tr>
<tr>
<td>Adverse conception outcomes</td>
<td>62 (17%)</td>
<td>83 (23%)</td>
<td>.03</td>
</tr>
<tr>
<td>Adverse pregnancy outcomes</td>
<td>58 (19%)</td>
<td>70 (25%)</td>
<td>.058</td>
</tr>
<tr>
<td>Complications of pregnancy</td>
<td>47 (16%)</td>
<td>68 (25%)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th># Studies</th>
<th>95 %CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth</td>
<td>1.85</td>
<td>22</td>
<td>1.67–2.05</td>
</tr>
<tr>
<td>SGA</td>
<td>1.36</td>
<td>13</td>
<td>1.16–1.60</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1.57</td>
<td>10</td>
<td>1.03–2.38</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
<td>1.29 (publication bias)</td>
<td>11</td>
<td>1.05–1.58</td>
</tr>
</tbody>
</table>

23 studies
15,007 women with IBD
5449 CD, 6559 UC
4,614,271 controls
<table>
<thead>
<tr>
<th></th>
<th>CD Preganancies with Disease Activity Outcome/Total (%)</th>
<th>CD Preganancies with NO Disease Activity Outcome/Total (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
<th>Subanalysis: Crude RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW</td>
<td>4/69 (5.8)</td>
<td>8/83 (9.6)</td>
<td>0.6 (0.2–2.0)</td>
<td>0.2</td>
<td>1.1 (0.3–4.0)</td>
</tr>
<tr>
<td>LBW at term</td>
<td>1/62 (1.6)</td>
<td>3/77 (3.9)</td>
<td>0.4 (0.0–4.0)</td>
<td>0.4</td>
<td>0.9 (0.1–8.5)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>8/70 (11.4)</td>
<td>6/82 (7.3)</td>
<td>1.6 (0.5–5.0)</td>
<td>2.4</td>
<td>3.4 (1.1–10.6)</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>3/71 (4.2)</td>
<td>5/86 (5.8)</td>
<td>0.7 (0.2–3.1)</td>
<td>0.8</td>
<td>0.4 (0.0–3.9)</td>
</tr>
</tbody>
</table>

*Adjusted for mother’s age, parity, maternal smoking during pregnancy, use of drugs during pregnancy (5-ASA, local or systemic steroid or immunosuppressive drugs), disease duration of CD (<5 yr, ≥5 yr), and calendar period of birth

**Subanalysis comparing the birth outcomes in women with moderate-high disease activity at any time during pregnancy with outcomes in women with inactive disease


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### Increased Risk of Pregnancy Complications in IBD

- **On systemic corticosteroids:**
  - Severe pre-eclampsia (HR 17.4, 95% CI 3.72-81.4)
  - Preterm premature rupture of membranes (HR 24, 95% CI 6.28-91.5)
  - Medically indicated preterm delivery (HR 7.54, 95% CI 2.51-22.6)

- **On local corticosteroids**
  - Preterm premature rupture of membranes
  - Medically indicated preterm delivery

The Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) Registry

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Medication Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not exposed</td>
<td>No IM or Biologics</td>
</tr>
<tr>
<td>Group A</td>
<td>Immunomodulator (IM) AZA/6MP</td>
</tr>
<tr>
<td>Group B</td>
<td>Biologic agent IFX, ADA, CZP</td>
</tr>
<tr>
<td>Group AB</td>
<td>Combination therapy (IM + biologic)</td>
</tr>
</tbody>
</table>

Mahadevan U et al. PIANO: a 1000 patient prospective registry of pregnancy out come in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterology 2012 142(5 Suppl. 1) S149 (omes in women with IBD exposed to abstract).

The PIANO Registry

- 33 (4.1%) spontaneous abortions, 37 (4.6%) congenital abnormalities
- Thiopurines and anti-TNF not associated with an increase in any complication, SAB, CA, preterm birth, IUGR, c-section or NICU stay
- Infant height, weight and developmental milestones, adjusted for disease activity, were similar among infants in all groups at 4, 9 and 12 months of age

Mahadevan U et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterology 2012 142(5 Suppl. 1) S149 (Abstract).
How will pregnancy affect IBD?

Disease Activity at Conception Dictates Course in Pregnancy

- **UC**
  - If active at the time of conception\(^1\)
    - 45% worsen
    - 24% stay the same (active, stable)
    - 25% improve
  - When remission at conception, risk of relapse during pregnancy is 33%\(^4\)

- **CD**
  - If active at the time of conception\(^1\)
    - 1/3\(^{rd}\) worsen
    - 1/3\(^{rd}\) stay the same (active, stable)
    - 1/3\(^{rd}\) improve
  - When remission at conception, risk of relapse during pregnancy 20% in CD\(^4\)

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Risk of Relapse | RR (95% CI)
---|---
Pregnant women with UC | 
During pregnancy | 
• 1st Trimester | 2.19 (1.25–3.97) • 8.80 (2.05–79.3) P < 0.0004
• 2nd Trimester | • 2.84 (1.2–7.45) P = 0.0098
Postpartum | 6.22 (2.05–79.3) P = 0.0004


Active disease at conception results in higher chance of active disease in pregnancy

- **UC**
  - Active disease at conception → higher risk ratio of active disease in pregnancy (55%) c/w those in remission at conception (36%) [RR 2.0 95% CI 1.5-3 P<0.001]

- **CD**
  - As above; RR 2.0, 95% CI: 1.2–3.4, P = 0.006

IBD medications and pregnancy

Active IBD not the treatment for IBD is most harmful to pregnancy

Aminosalicylates in Pregnancy

- Safety of 5-ASA compounds demonstrated in several trials
- Women taking 5-ASA for IBD have no higher incidence of fetal abnormalities than in normal healthy women\(^1,2,3,4\)


Dibutyl phthalate (DBP)

- Coating of Asacol & Asacol HD
- External and skeletal malformations and urogenital defects in male offspring of exposed mothers in rats
- Can inhibit in utero reproductive development and negatively affect neurodevelopment
- Possible association with developmental problems

DBP and Pregnancy

- Caution patients regarding this effect
- Consider switching to non-DBP mesalamine prior to pregnancy
Sulfasalazine in Pregnancy

- Sulfasalazine may inhibit absorption and lower serum concentrations of folic acid
  - When attempting to conceive and during pregnancy, increase folic acid supplementation to 2mg daily

Thiopurines in Pregnancy

- Teratogenic effects of AZA have been described in animals
- There is transfer of AZA and its metabolites to the fetus
  - Oral bioavailability is low
  - 6-thioguanine crosses the human placenta

Thiopurines and the PIANO registry

- >335 exposed to AZA/6MP during pregnancy
  - No increased risk of congenital malformations or pregnancy complications
  - Adjusting for disease activity, those infants exposed have equivalent or better achievement of developmental milestones
  - Infections at 9-12 months age more common in 107 infants exposed combination therapy with thiopurine (RR 1.50, 95% CI 1.08-2.09)¹


Thiopurines in Pregnancy

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year of Publication</th>
<th>Type of Study</th>
<th>Pregnancies exposed to Azathioprine or 6MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Francella</td>
<td>2003</td>
<td>Retrospective</td>
<td>39</td>
</tr>
<tr>
<td>Norgard</td>
<td>2007</td>
<td>Retrospective</td>
<td>20</td>
</tr>
<tr>
<td>Cleary</td>
<td>2009</td>
<td>Retrospective</td>
<td>324</td>
</tr>
<tr>
<td>Coelho</td>
<td>2010</td>
<td>Prospective, Retrospective</td>
<td>86</td>
</tr>
<tr>
<td>Shim</td>
<td>2011</td>
<td>Retrospective</td>
<td>19</td>
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</table>

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year of Publication</th>
<th>Type of Study</th>
<th>Pregnancies with Paternal Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Francella</td>
<td>2003</td>
<td>Retrospective</td>
<td>37</td>
</tr>
<tr>
<td>Rajapakse</td>
<td>2000</td>
<td>Retrospective</td>
<td>13</td>
</tr>
<tr>
<td>Teruel</td>
<td>2010</td>
<td>Retrospective</td>
<td>46</td>
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</table>

Thiopurines in Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>OR in WOMEN Exposed to Thiopurines</th>
<th>OR in MEN Exposed to Thiopurines</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW</td>
<td>1.01 (95% CI 0.96, 1.06, P=0.831)</td>
<td></td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.67 (95% CI 1.26, 2.20, P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>Congenital abnormality</td>
<td>1.45 (95% CI 0.99, 2.13, P=0.055)</td>
<td>1.87 (95% CI 0.67, 5.25, P=0.236)</td>
</tr>
</tbody>
</table>


Thiopurines and Preterm Birth

- 1833 UC, 1220 CD
- Thiopurine exposure increased risks for preterm birth regardless of disease activity
  - stable (aOR, 2.41; 95% CI, 1.05-5.51)
  - flaring disease (aOR, 4.90; 95% CI, 2.76-8.69)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Exposed to Thiopurines (%)</th>
<th>Not Exposed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortions</td>
<td>8.6</td>
<td>12.3</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>4.3</td>
<td>9.2</td>
</tr>
<tr>
<td>Elective abortions</td>
<td>1.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Fetal loss</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Premature rupture of membranes</td>
<td>2.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Infections</td>
<td>1.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Preterm labor menace</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Essential thrombocythemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fetal macrosomia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>4.2</td>
<td>9</td>
</tr>
<tr>
<td>ICU admission</td>
<td>1.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Thiopurines in Pregnancy

- Based on most of the literature, thiopurines are safe during pregnancy\(^1,2,3\)

- Due to slow onset of action and idiosyncratic reactions (bone marrow suppression, pancreatitis, hepatotoxicity, allergic reactions, and opportunistic infections), *avoid initiation* during pregnancy

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\(^1\)Mahadevan U and Kane S.  American gastroenterological association institute technical review on the use of gastrointestinal medications in pregnancy.  Gastroenterology 2006;131:283-311.


\(^3\)Nguyen et al.  The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy
Factors to Consider about Thiopurines in Pregnancy

- Maternal metabolism of thiopurine altered throughout pregnancy and returns to preconception levels after delivery
  - Consider measuring 6-thioguanine nucleotide and 6-methylmercaptopurine levels during pregnancy
  - e.g. if active disease


Other Factors to Consider about Thiopurines in Pregnancy

- Case report of 30 patients treated during pregnancy
  - 60% of newborns had mild anemia at birth
    - Result of 6-thioguanine crossing the placenta
  - Suggestion to evaluate for signs of anemia in newborns of mothers who used thiopurines

Methotrexate (MTX) in Pregnancy

- Contraindicated in pregnancy


Nguyen et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy

Cyclosporine in Pregnancy

- Majority of experience in pregnancy with this is from transplant literature
- Increased rates of pregnancy complications, preterm birth and low birth weight

Biologic Therapy in Pregnancy

Infliximab (IFX) and Pregnancy

- **TREAT Registry**
  - 117 of a total 168 pregnancies had prior IFX exposure
  - Rate of miscarriage (10 vs 6.7%) and neonatal complications (6.9 vs 10%) not significantly different
  - No reports of fetal malformations

- **Infliximab Safety Database**
  - 96 women directly exposed to IFX during pregnancy
  - Exposure mainly during conception and 1st trimester
  - No significant differences in live births, miscarriages, therapeutic terminations

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IFX in Pregnancy

- 10 women with active CD during pregnancy
  - All 10 pregnancies resulted in live births
  - 0 congenital malformations, IUGR or SGA
  - 3 preterm (<37wks) births
  - 1 infant with LBW (<2500 grams)


IFX in Pregnancy

- Review of FDA database of reported adverse events with etanercept, infliximab, and adalimumab 1999-2005
- > 120,000 adverse events reviewed
  - 61 congenital anomalies in 41 children born to mothers taking a TNF antagonist
    - 19 mothers were taking infliximab
    - None of mothers taking adalimumab
    - 19 (56%) part of the VACTERL spectrum

IFX in Pregnancy

- The PIANO Registry
  - No increased risk of adverse events in congenital anomalies, infant growth status or developmental progress

Adalimumab (ADA) in Pregnancy

- The Organization for the Teratological Information Specialists (OTIS) Registry¹
  - Prospective study
  - No significant differences

- Jurgens et al²
  - Review of 132 pregnancies with ADA exposure
  - No fetal abnormalities

- The PIANO Registry³,⁴
  - No increased risk of adverse events in congenital anomalies, infant growth status or developmental progress

³Mahadevan U et al. PIANO a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterology 2012 142(Suppl. 1) S149 (Abstract).
⁶Nguyen et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy.
Certolizumab Pegol (CZP) in Pregnancy

- Case Report
  - Dosing:
    - 11 injections prior to conception; One injection during 1st trimester; not continued as pt asymptomatic; 31 wks GA, had a flare; given single dose w/ improvement
    - Delivered normal full term female infant
    - Normal growth and development at 1 month age

- The PIANO Registry
  - No increased risk of adverse events in congenital anomalies, infant growth status or developmental progress

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Anti-TNF and Pregnancy

- Meta-analysis of 5 studies with 1216 participants
- No differences in:
  - total unfavorable pregnancy outcomes
  - abortion
  - preterm birth
  - low birth weight
  - congenital malformation
Placental Transfer of Biologics

- Immunoglobulins transported across placenta to provide immunity to the newborn by neonatal Fc receptor during the 2nd & 3rd trimester\(^1,2\)
  - IgG1 are most efficiently transported – eg IFX, ADA
- CZP has poor placental transport in 2nd and 3rd trimester due to missing Fc portion\(^3,4\)
  - Low levels of drug in cord blood seen however\(^4,5\)

\(^2\) Kane SV and Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. AM J Gastroenterol 2009; 104:228-33.

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Placental Transfer of TNF\(\alpha\) Therapy

<table>
<thead>
<tr>
<th></th>
<th>IFX</th>
<th>ADA</th>
<th>CZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pregnant women with IBD using med</td>
<td>11</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Median time from last dose to delivery</td>
<td>35 days</td>
<td>5.5 wks</td>
<td>19 days</td>
</tr>
<tr>
<td>Median ratio of cord to maternal drug level (%)</td>
<td>160%</td>
<td>179%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Time for drug to become undetectable</td>
<td>2-7 months</td>
<td>atleast 11 weeks from birth</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P T</th>
<th>IFX Dose</th>
<th>Co-meds</th>
<th>GA IFX d/c’d</th>
<th>GA Birth</th>
<th>BW (g)</th>
<th>CM</th>
<th>IFX level cord (mg/mL)</th>
<th>IFX level mother (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5mg/kg q8wks</td>
<td>None</td>
<td>21</td>
<td>37</td>
<td>2650</td>
<td>None</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>2</td>
<td>5mg/kg q8wks</td>
<td>None</td>
<td>26</td>
<td>36</td>
<td>4030</td>
<td>None</td>
<td>13</td>
<td>4.9</td>
</tr>
<tr>
<td>3</td>
<td>5mg/kg q8wks</td>
<td>MTX 2 months prior to conception</td>
<td>26</td>
<td>41</td>
<td>3030</td>
<td>Polydactyly left hand</td>
<td>5.5</td>
<td>2.4</td>
</tr>
<tr>
<td>4</td>
<td>10mg/kg q8wks</td>
<td>AZA 2mg/kg</td>
<td>30</td>
<td>39</td>
<td>3185</td>
<td>None</td>
<td>13.7</td>
<td>5 (P = 0.032)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th># live births</th>
<th># d/c &lt;30wk GA</th>
<th>Flares after d/c</th>
<th>Early d/c &gt;10wks before delivery</th>
<th>Late d/c ≤10wks before delivery</th>
<th>Mean cord level mg/mL (IFX 12, ADA 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX</td>
<td>17</td>
<td>12</td>
<td>0</td>
<td>6</td>
<td>Overall 6.4 +1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Early d/c 2.8 +1.1</td>
<td>Late d/c 10 ± 2.3</td>
<td>P = .02</td>
</tr>
<tr>
<td>ADA</td>
<td>11</td>
<td>11</td>
<td>2</td>
<td>6</td>
<td>1.7 +0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(one sample with undetectable level; d/c'd 22wkGA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consequences of Placental Transfer

- Case report
  - Infant exposed to IFX (10mg/kg q8 wks for CD) during gestation
  - Healthy boy delivered 36 wks
  - No breastfeeding
  - Vaccinated with BCG at 3 months

Died of disseminated BCG at 4.5 months


**PIANO Registry Nov 2013**

- 1097 completed pregnancy
- 1039 live births
- 422 T3 biologic exp
  - 214 IFX
  - 117 ADA
  - 89 CZP
  - 9 NAT

- 3rd trimester exposure did not increase risk of preterm birth, the risk of disease activity, and the risk of infant infections

<table>
<thead>
<tr>
<th># observations</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth</td>
<td>1019</td>
<td>1.3</td>
</tr>
<tr>
<td>Disease Activity T3</td>
<td>977</td>
<td>0.7</td>
</tr>
<tr>
<td>Disease Activity PP</td>
<td>767</td>
<td>1.2</td>
</tr>
<tr>
<td>Infection Month 4</td>
<td>1009</td>
<td>0.9</td>
</tr>
<tr>
<td>Infection Month 9</td>
<td>741</td>
<td>1.1</td>
</tr>
<tr>
<td>Infection Month 12</td>
<td>678</td>
<td>1.1</td>
</tr>
</tbody>
</table>


Prospective study of 80 pregnant women with IBD
36 ADA, 44 IFX, 39 with combination IM
Levels q3 month until no drug detected

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>IFX</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant:mother</td>
<td>1.21 (95% CI 0.94-1.49)</td>
<td>1.97 (95% CI 1.5-2.43)</td>
<td></td>
</tr>
<tr>
<td>drug conc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to drug</td>
<td>4 months (95% CI 2.9-5.0)</td>
<td>7.3 months (95% CI 6.2-8.3)</td>
<td></td>
</tr>
<tr>
<td>clearance in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infant (mean)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR Infection</td>
<td></td>
<td></td>
<td>2.7 (95% CI 1.09-6.78) c/w mono</td>
</tr>
</tbody>
</table>

Considerations for Timing
Doses in view of Placental Transfer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Conception</th>
<th>1st Trimester</th>
<th>2nd Trimester</th>
<th>3rd Trimester</th>
<th>Post-partum</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Last dose</td>
<td>Resume</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30-32 wks GA</td>
<td></td>
</tr>
<tr>
<td>ADA</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Last dose</td>
<td>Resume</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36-38 wks GA</td>
<td></td>
</tr>
<tr>
<td>CZP</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
</tr>
</tbody>
</table>
Recommendations for Infants Due To Placental Transfer

- Long term effects of placental transfer and exposure in utero not known
- Avoid live vaccines in an infant for the first 6-12 months who were exposed to IFX or ADA in utero or who have detectable levels


Combination therapy

- Risk of infection
- Possible preterm birth (OR 2.4; 95% CI 1.3-4.3) and any pregnancy complication (OR 1.7; 95% CI 1.0-2.2)

Consider temporarily stopping the thiopurine prior to conception

1 Mahadevan U et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterology 2012 142(5 Suppl. 1) S149 (Abstract).
Nguyen et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy.
Natalizumab in Pregnancy

- There have been no adequate and well-controlled trials in pregnant women (MS literature)
- Review of the natalizumab global safety data base\(^1,2\)
  - 164 pregnancies with natalizumab exposure
  - No increase in birth defects
- The PIANO registry\(^2,3\)
  - No observed increased rates of adverse events in congenital anomalies or growth impairment or developmental delay

\(^3\)Mahadevan U et al. A 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterology 2012 142(Suppl. 1):S49 (Abstract).

Vedolizumab in Pregnancy

- Limited pregnancy safety data
- Half-life is more than 3 times longer than that of IFX

\(^5\)Nguyen et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel disease in Pregnancy
## Timing Doses in view of Placental Transfer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Conception</th>
<th>1st Trimester</th>
<th>2nd Trimester</th>
<th>3rd Trimester</th>
<th>Post-partum</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFX</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Last dose 30-32 wks GA</td>
<td>Resume</td>
</tr>
<tr>
<td>ADA</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Last dose 36-38 wks GA</td>
<td>Resume</td>
</tr>
<tr>
<td>CZP</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
</tr>
<tr>
<td>GOL</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Last dose 34-36 wk</td>
<td>Resume</td>
</tr>
<tr>
<td>NAT</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Last dose week 36</td>
<td>Resume</td>
</tr>
<tr>
<td>VEDO</td>
<td>Continue</td>
<td>Continue</td>
<td>Continue</td>
<td>Last dose 30-32 wk</td>
<td>Resume</td>
</tr>
</tbody>
</table>

## Steroids in Pregnancy

- Short acting prednisone, prednisolone and methylprednisolone more efficiently metabolized by placenta and may result in lower fetal exposure than dexamethasone and betamethasone
Steroids in Pregnancy

- Oral clefts in newborns seen if corticosteroid use was in the first trimester\(^1,2,3,4\)


Steroids in Pregnancy

- Exposure to corticosteroids during the first trimester occurred in 51,973 of pregnancies
  - Risk of orofacial clefts: OR 1.05 95% CI 0.8-1.38

Steroids and Pregnancy – PIANO Registry


Budesonide and Pregnancy

What mode of delivery is best?

Decision should be made based on discussion between the patient, her partner, her obstetrician & gastroenterologist.

- Patient’s with IBD undergo c-section more frequently than non-IBD patients\(^1,2,3,4\)
  - Concern for vaginal deliveries in
    - CD patients with perianal disease
    - UC s/p IPAA

\(^4\) Mahadevan U, Martin CF, Dubinsky M, et al. Exposure to anti-TNFα therapy in the third trimester of pregnancy is not associated with increased adverse outcomes: results from the PANDO registry (abstract). Gastroenterology 2014;146:S-170.
Breastfeeding and IBD

IBD flares that occur during breastfeeding usually occur due to stopping medications and not due to actual breastfeeding\(^1,2\)

Need to weigh risks and benefits of each medication and breastfeeding


Aminosalicylates and Breastfeeding

- Case report of breastfed infant developing severe watery diarrhea after mother used rectal 5-ASA
- Sulfonamides have bilirubin displacing ability
  - Sulfapyridine less likely to do so
  - Amount transferred to breast milk negligible with regards to kernicterus risk


AZA and Breastfeeding

<table>
<thead>
<tr>
<th>Indication</th>
<th>Meds</th>
<th>GA at delivery</th>
<th>Infant exposure c/w mom’s wt-adjusted dose (%)</th>
<th>Adverse Effects in Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SLE</td>
<td>azathioprine 100 mg/day; warfarin, prednisone, calcitriol, calcitonin, acetaminophen, calcium, vitamins C and E</td>
<td>full term</td>
<td>&lt;0.09</td>
<td>None (followed to 15 mo; breastfed until 12 mo)</td>
</tr>
<tr>
<td>2 SLE</td>
<td>azathioprine 100 mg/day; warfarin, prednisone, calcium, levothyroxine</td>
<td>36wk</td>
<td>&lt;0.09</td>
<td>None (followed to 2 months)</td>
</tr>
<tr>
<td>3 liver transplant</td>
<td>azathioprine 75 mg/day; cyclosporine, prednisone</td>
<td>full term</td>
<td>-</td>
<td>None (followed to 1 month)</td>
</tr>
<tr>
<td>4 renal transplant</td>
<td>azathioprine 50 mg/day; cyclosporine, prednisone</td>
<td>36 wk</td>
<td>-</td>
<td>None (followed to 2 months)</td>
</tr>
</tbody>
</table>

**AZA and Breastfeeding**

- AZA dose 1.2–2.1 mg/kg/day
- All had the wild-type TPMT genotype

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose of azathioprine (mg/day)</th>
<th>GA at Delivery (wks)</th>
<th>BW (g)</th>
<th>Neonatal age at the time of blood sampling</th>
<th>6-MP and TGN levels (nanograms/ml)</th>
<th>White cell counts (3*10⁹/l)</th>
<th>Neutrophil counts (3*10⁹/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SLE</td>
<td>100</td>
<td>38</td>
<td>3515</td>
<td>Day 8</td>
<td>0 and 0</td>
<td>10.7</td>
<td>3.5</td>
</tr>
<tr>
<td>2 SLE</td>
<td>100</td>
<td>32</td>
<td>1940</td>
<td>Day 1&lt;br&gt;Day 2&lt;br&gt;Day 10</td>
<td>0 and 0</td>
<td>4.6</td>
<td>2.3</td>
</tr>
<tr>
<td>3 Renal transplant</td>
<td>100</td>
<td>34</td>
<td>1790</td>
<td>Day 7</td>
<td>0 and 0</td>
<td>9.6</td>
<td>5.2</td>
</tr>
<tr>
<td>4 SLE</td>
<td>100</td>
<td>37</td>
<td>3140</td>
<td>Day 1&lt;br&gt;Day 9</td>
<td>0 and 0</td>
<td>26.4</td>
<td>14</td>
</tr>
<tr>
<td>5 SLE</td>
<td>100</td>
<td>39</td>
<td>2750</td>
<td>Day 28</td>
<td>0 and 0</td>
<td>8.3</td>
<td>1.7</td>
</tr>
<tr>
<td>6 SLE</td>
<td>100</td>
<td>37</td>
<td>3140</td>
<td>Day 20</td>
<td>0 and 0</td>
<td>25.5</td>
<td>20.4</td>
</tr>
<tr>
<td>7 SLE, lupus nephritis</td>
<td>100</td>
<td>33</td>
<td>1940</td>
<td>Day 2&lt;br&gt;Day 8</td>
<td>0 and 0</td>
<td>20.6</td>
<td>14.8</td>
</tr>
<tr>
<td>8 SLE, lupus nephritis</td>
<td>100</td>
<td>39</td>
<td>2750</td>
<td>No blood sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Renal transplant</td>
<td>75</td>
<td>39</td>
<td>3630</td>
<td>No blood sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 CD</td>
<td>150</td>
<td>37</td>
<td>3170</td>
<td>No blood sample</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


AZA and Breastfeeding

Method:
- 8 lactating women with IBD receiving maintenance therapy with AZA 75–200 mg daily
- Milk and plasma samples were obtained 30 and 60 min after drug administration and hourly for the following 5 hours

Results
- The major part of 6-MP in breast milk is excreted within the first 4 h after drug intake
- On the basis of maximum concentration measured, the infant ingests mercaptopurine of <0.008 mg/kg bodyweight/24 h


PIANO Registry

- No increased risk of infection or developmental delay among nursing infants whose mothers took thiopurines

Cyclosporine and Breastfeeding

- Not recommended
- Study
  - 5 mother-infant pairs
  - Wide range of infant exposures to the drug in the milk
  - 1 infant had therapeutic blood concentrations despite low concentrations of the drug in the milk


IFX from placental transfer not breastfeeding

<table>
<thead>
<tr>
<th></th>
<th>IFX level Mother’s Serum (µg/mL)</th>
<th>IFX level Breast Milk (µg/mL)</th>
<th>IFX level Infant Serum (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>40</td>
<td>Not detectable</td>
<td>39.5</td>
</tr>
<tr>
<td>10 weeks</td>
<td>9.3</td>
<td>Not detectable</td>
<td>Infant IFX serum levels declining with time</td>
</tr>
<tr>
<td>13 weeks</td>
<td>84</td>
<td>Not detectable</td>
<td></td>
</tr>
</tbody>
</table>

IFX Not Detected in Breast Milk

- **Case report**
  - **Dosing:**
    - Prior to pregnancy: 10mg/kg every 4 wks and mesalamine
    - During pregnancy: 6 infusions; Last infusion 2 wks prior to delivery
  - Infant born full term and healthy
  - Breast milk collected
    - Baseline – No IFX
    - Given dose & milk checked daily for 30 days - no IFX
  - At 27 mo, no developmental abnormalities were noted in the child


IFX Detected in Breast Milk

- **Methods**
  - Serum & breast milk obtained post-partum from 3 breast-feeding CD pts before and after re-initiation of IFX

- **Results**
  - IFX levels in breast milk reached 101ng/ml within 2-3 days of the infusion
  - IFX levels in breast milk were ~ 1/200th the level in blood
  - Amount transferred in breast milk unlikely to cause infant systemic immune-suppression

ADA Detected in Breast Milk

- **Case Report**
  - Pt w Crohn's ileitis of 7 yrs. Conceived while in remission induced by ADA (started 8 months prior to conception); ADA d/c'd 30 wks GA
  - Healthy infant delivered 38 wk GA
  - Flared 4 wks postpartum -> given ADA dose; Was breastfeeding

- **Methods**
  - Blood & breast milk samples obtained before and every 2 days for 8 days after dose of ADA 40mg subcut given

- **Results**
  - Prior to injection, levels were nil in breast milk and serum
  - Following injection, ADA serum level increased and peaked on day 3 at 4300 ng/mL and declined thereafter
  - ADA levels in breast milk <1/100th of serum
  - Breast milk ADA level rose from undetectable and reached 31 ng/mL on day 6 post injection


CZP not detected in Breast Milk

- **Case report**
  - Measured breast milk levels at 4 hours, 3 days and 6 days after the first postpartum dose
  - Undetectable levels in all samples

PIANO Registry

- 10/2013-10/2014, 20 mothers submitted BM samples:
  - 11 infliximab (IFX)
  - 6 adalimumab (ADA)
  - 3 certolizumab (CZP)


PIANO Registry – Anti-TNF and BM

- IFX: Maximum BM concentration (90-591 ng/mL) was detected between 24-48 hours after infusion.
- ADA and CZP were not detected in BM at any of the time points.

PIANO Registry

- No increased risk of infection or developmental delay among nursing infants whose mothers took anti-TNF agents


Prednisone and Breastfeeding

- Secreted in breast milk\textsuperscript{1,2,3}
- For doses of Prednisolone 80mg daily $\rightarrow <0.1\%$ of the dose ingested by infant\textsuperscript{1}
- Minimize exposure of prednisolone higher doses ($>40\text{mg}$) if avoid breastfeeding during first 4 hours after dose\textsuperscript{1}

\textsuperscript{2}Greenberger et al. Pharmacokinetics of prednisolone transfer to breast milk. Clin Pharm Ther 1993 53(3) 324-328.
Budesonide and Breastfeeding

- Methods:
  - 8 women and their infants age 2-6 months
  - Milk and plasma samples collected up to 8 hours after budesonide treatment (200mg and 400mg)
  - Pharmacokinetic parameters calculated from budesonide milk and plasma concentrations. Infant exposure estimated based on average milk budesonide concentrations

- Results:
  - Mean milk/plasma ratio was 0.46
  - Estimated daily infant dose 0.3% of daily maternal dose
  - The average plasma concentration in infants ~1/600th of the concentrations observed in maternal plasma


Summary

- The most important factor in optimizing pregnancy and neonatal outcomes is keeping disease in remission
- Pre-conception counseling should be done routinely
- The only maintenance medications contraindicated in pregnancy are Methotrexate and Thalidomide
- Risks and benefits of medications in pregnancy and breastfeeding must constantly be assessed
Summary

Management should be multi-disciplinary including the patient’s primary care provider, her gastroenterologist and her high-risk obstetrician.