FERTILITY AND PREGNANCY IN IBD

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Objectives

- Fertility
- Risk of IBD in children
- Effect of pregnancy on disease activity
- Symptom evaluation during pregnancy
- Medical treatment during pregnancy and breast feeding
Pregnancy in IBD

- Pregnancy is safe and outcomes are good when disease is in remission and there is close monitoring and good communication.

- Risk of disease activity outweighs risk of *most* medications.
  - Deep remission prior to conception
  - Stable medication regimen

Julsgaard, IBD, 2011
Fertility in women with IBD

- Reduced with high disease activity
  - Fever, high levels of inflammation
  - Poor nutrition
  - Involvement of pelvic organs
- In patients with inactive disease, prior pelvic surgery is a major risk factor for infertility
  - Ileoanal pouch/ J pouch
  - Proctectomy
Pregnancy after J pouch

Cumulative incidence of pregnancy vs. time to pregnancy (months)

- Dashed line: Before diagnosis reference
- Dotted line: Before surgery
- Solid line: After surgery

Olson, Gastro, 2002
Pregnancy after laparoscopic J pouch

![Graph showing the proportion of patients pregnant over time, comparing laparoscopic IPAA and open IPAA procedures. The log-rank test shows a statistically significant difference (P=0.023).](image-url)
Male fertility

LOW RISK

- 5-ASA
- Thiopurines
- Anti-TNF
- Antibiotics
- ?Vedolizumab

AVOID

- Sulfasalazine
  - Low sperm count, abnormal shape and mobility
- Methotrexate
  - Low sperm count
  - Reversible 2-3 months

Toovey, Gut, 1981
Dejaco, Gastro, 2001
French, Can Fam Phys, 2003
Akbari, IBD, 2013
Genes associated with IBD

## Risk of IBD in offspring

<table>
<thead>
<tr>
<th>Risk to offspring</th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jewish</td>
<td>7.5%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Non-Jewish</td>
<td>5%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

- C-section *does not* increase risk of IBD
- Breast feeding may reduce risk of IBD

Yang, Gut, 1993  
Bernstein, CGH, 2016  
Castiglione, JCC, 2012
Effect of pregnancy on disease activity

- **UC**
  - Inactive: unchanged
  - Active: increased, decreased

- **CD**
  - Inactive: unchanged
  - Active: increased, decreased

Adapted from *Ulcerative Colitis*, Lichtenstein, 2011
Active disease increases risk of preterm birth

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Birth Rate</td>
<td>1.1</td>
<td>0.3-4</td>
</tr>
<tr>
<td>Preterm Birth</td>
<td>3.4</td>
<td>1.1-10.6</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
<td>0.4</td>
<td>0-3.9</td>
</tr>
</tbody>
</table>

Norgard, Am J Gastro, 2007
Medications in pregnancy

LOW RISK

• Thiopurines
• Anti-TNFs
• Non-Asacol 5-ASAs
• Sulfasalazine
  • add folic acid 2-3 mg per day
• Steroids
  • Avoid 1st trimester
  • Increased risk gestational diabetes

AVOID

• Methotrexate
  • Causes abortion
  • Birth defects- skeletal defects, cleft palate
• Thalidomide
  • Birth defects-limb malformations, heart, kidney, digestive defects
• ? Asacol/ Asacol HD
  • Dibutyl Phthalate – uro-gential abnormalities

Lin, DDW 2014
Nguyen, Gastro, 2016
## Placental Transfer of anti-TNFs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Infant Cord Blood (10)</th>
<th>Time to clear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>&gt; mother</td>
<td>up to 7 months</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>&gt; mother</td>
<td>up to 6 months</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>&lt; 2 mcg/mL</td>
<td>--</td>
</tr>
</tbody>
</table>

Mahadevan, Clin Gastro Hep, 2013
PIANO: Pregnancy in IBD and Neonatal Outcomes

- Large prospective cohort of pregnant woman with IBD to determine effect of medications on pregnancy outcomes
- Enrolled women took serial surveys during each trimester and newborns followed until age 4
- Groups
  - Unexposed: (can include steroids, 5-ASA, antibiotics)
  - Group A: Thiopurine
  - Group B: Biologics (IFX, ADA, CZP, NAT)
  - Group AB: Combination TP/biologic
- Interim analysis
## The Piano Study: Adverse Pregnancy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Group A (aza) RR (CI)</th>
<th>Group B (bio)</th>
<th>Group AB (combo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Complication</strong></td>
<td>1.1</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Spontaneous Abortion</strong></td>
<td>1.2</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Preterm Birth</strong></td>
<td>1.0</td>
<td>0.9</td>
<td><strong>2.6</strong></td>
</tr>
<tr>
<td><strong>Low Birth Weight</strong></td>
<td>0.9</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Cesarean section</strong></td>
<td>1.1</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>NICU</strong></td>
<td>1.2</td>
<td>1.3</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Congenital Anom</strong></td>
<td>1.3</td>
<td>1.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Mahadevan, AIBD, 2015
PIANO: infections increased in offspring on combination therapy

- Certolizumab excluded
- No difference in serious infections
- Infections mostly ear infections, URIs

<table>
<thead>
<tr>
<th>Adjusted for Preterm birth</th>
<th>Month 4 RR (CI)</th>
<th>Month 9</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopurine (A)</td>
<td>1.1</td>
<td>1.2</td>
<td>0.98</td>
</tr>
<tr>
<td>Biologic (B)</td>
<td>1.1</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Combo(AB)</td>
<td>1.2</td>
<td>1.2</td>
<td>1.35 **</td>
</tr>
</tbody>
</table>

Mahadevan,
Exposure to anti-TNF in third trimester is not associated with adverse outcomes

Outcomes not associated with Biologic exposure during pregnancy

<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth</td>
</tr>
<tr>
<td>Disease activity in 3rd trimester or 4 months post-partum</td>
</tr>
<tr>
<td>Infections out to 1 year of age</td>
</tr>
<tr>
<td>Controlled for age, preterm birth, certolizumab pegol use</td>
</tr>
</tbody>
</table>

Mahadevan, DDW, 2014
Normal developmental milestones in offspring of patients with IBD on medications

Pregnant women with IBD enrolled in multisite national prospective cohort (PIANO) N=1289

Completed pregnancies N=1,085

Live births N=1,039*

- AZA/6MP (n=230)
- Biologic-exposed (n=392)
- Combination (AZA/6MP + biologic) (n=107)
- Reference (unexposed) (n=356)

*417 patients completed 1-year questionnaire

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

- Equivalent or better achievement using Denver Childhood Developmental Score (months 4, 9, 12) and Ages & Stages Questionnaire (Year 1, 2, 3, 4)
- Controlled for preterm birth
- No change when controlled for maternal income and education level

Mahadevan, DDW, 2014
Biologic management during pregnancy

- Certolizumab is a good choice in women of child-bearing age
- Switching biologics is not recommended before or during pregnancy due to risk for flare
- Combo therapy with anti-TNF and thiopurine individualized
- Measures to limit placental transfer
  - Adjust schedule to stop Infliximab at week 32
  - Stop Adalimumab week 36-38
  - Continue Certolizumab throughout pregnancy
  - Do not stop medications if flaring
- Communicate with pediatrician regarding *in utero* exposure and avoidance of live virus vaccines x 6 months

Mahadevan, Clin Gastro Hep, 2013
Ng, Exp Rev Clin Imm, 2012
Symptoms may be difficult to interpret during pregnancy

- Abd pain and changes in bowel habits are common during pregnancy
- Normal changes in lab parameters
  - Decrease in blood counts, protein levels, increased inflammatory markers
- Alternative diagnoses during pregnancy
  - Gallstones
  - Preeclampsia
Diagnostics during pregnancy

- **Non-invasive testing**
  - C.Difficile, stool calprotectin

- **Imaging**
  - Abdominal ultrasound
  - MR Enterography
    - Avoid gadolinium in 1st trimester

- **Endoscopy**
  - Unsedated flex sig is low risk
  - If sedation required - anesthesia assisted with fetal monitoring
Mode of delivery

- Most patients should have delivery dictated by obstetric considerations
- C-section should be performed for:
  - Active perianal disease
  - Inactive perianal disease does not lead to development of disease after vaginal delivery
- C-section should be considered for:
  - Patients with a J pouch

Ilnyckji, Am J Gastro, 1999
Juhasz, DCR, 1995
Ravid, DCR, 2002
Breast feeding

• Compatible with most medications, but low levels of drug may be transferred in breast milk
• Despite relatively low risks of breast feeding, fewer women with IBD breastfeed
• For steroids and thiopurines, majority of drug transfers within 4 hours; can pump and discard milk with highest concentration of drug

Kane, Am J Gastro, 2005
Summary: pre-conception planning

- Meet with obstetrician (high risk) and gastroenterologist
- Confirm disease is in remission
  - Colonoscopy, imaging, baseline calprotectin
- If disease is not in remission, adjust medications to achieve remission prior to conception
- Update health maintenance
  - vaccines, colon cancer screening, pap smear, labs
- Review medications
  - Stop Methotrexate, Thalidomide x 3+ months
  - Change Asacol to alternative 5-ASA
  - Sulfasalazine add Folic acid 2-3 mg daily
  - Continue thiopurine, anti-TNF medications
  - Discuss risks/benefits of continuation of combination therapy with provider
Summary: care during and after pregnancy

- If no disease activity, meet with gastroenterologist once each trimester, more frequently if disease active
- Adjust Infliximab dosing so that last dose will be around week 32
- Vaccines: Flu, TDaP during third trimester
- Discuss mode of delivery with obstetrician
  - Active perianal disease, J pouch
- Choose a pediatrician and communicate with them regarding any biologic exposure in utero
- Avoid live virus vaccines for 6 months in infants exposed to Infliximab or Adalimumab, monitor for infections
SOMETHING MUST BE WRONG; I FEEL TOO GOOD.

PRENATAL PARANOIA.