Fertility and Pregnancy in IBD

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Mayo Clinic Rochester
Case

• 25 yr old with Crohn’s ileocolitis moved to town and wants to establish care
• Her disease is well controlled on a biologic
• She is newly engaged and wants to ask about her chances of getting pregnant, staying pregnant and how her baby will do
Your Reaction
After the Panic

• Fertility
• How will her pregnancy go?
• How will her IBD react?
• How healthy will her baby be?
Fertility in IBD

- Systematic review including 11 studies in non-surgical IBD patients
- In CD 17-44% reduction in fertility but linked to voluntary childlessness
- No decreased risk in UC
- In men with CD, 18-50% reduction but no difference in reproductive capacity

Fertility Rates in IBD

• UK population-based study fertility adjusted for age, smoking and SES
• 46.2 live births/1000 p-yrs in 10,000 IBD vs 49.3 in over 2 million healthy controls
• Fertility rate lower following flares and surgery by 16-20%

Adalimumab and Infertility

- Women with sub-fertility and Th1/Th2 cytokine elevation were treated with IVIG ± adalimumab
- 74 patients < 38 yrs old were allocated to one of four groups

<table>
<thead>
<tr>
<th></th>
<th>Implantation (%)</th>
<th>Pregnancy rate (%)</th>
<th>Live birth rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA + IVIG</td>
<td>59</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>IVIG</td>
<td>47</td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td>ADA</td>
<td>31</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Risk of Infertility in UC Increases Threefold After Ileal Pouch-anal Anastomosis (IPAA)*

* Compared to medical management

Waljee A. Gut. 2006;55:1575
Good News Ladies!

- IPAA patients 1998-2011 (22) compared with UC (49) and healthy controls (470) for successful IVF rates
- Cumulative live birth rate after 6 cycles in IPAA group 64%, UC 71%, controls 53%
- No difference either for oocytes retrieved, pregnancy rate or success after first cycle

Pabby V. *Am J Gastroenterol* 2015; 110:792-797.
Case 2: Conception

- 32F with 5 years of moderate to severe Crohn’s disease of the ileum and perineum complicated by perforating disease on azathioprine monotherapy requiring ileocolonic resection 1 year ago and a perianal fistula requiring seton placement, now removed.
  - She is maintained on infliximab 5 mg/kg every 8 weeks and azathioprine 2.5 mg/kg daily
  - She presents to the office and wants to know if she can stop her therapy in order to get pregnant and breastfeed
  - She plans to treat her disease with the specific carbohydrate diet (SCD)

What do you tell her?
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
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>
Effect of Pregnancy on IBD: Disease Activity at Conception


<table>
<thead>
<tr>
<th>Inactive</th>
<th></th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Relapse</td>
<td>73%</td>
<td>Worsened Activity</td>
</tr>
<tr>
<td>Relapse</td>
<td>27%</td>
<td>Continued Activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased Activity</td>
</tr>
</tbody>
</table>

n=186 n=93
Course of Disease During Pregnancy

- First prospective study of disease activity during pregnancy
- 92 CD, 117 UC matched with controls
- In CD 19% vs 18% flared during pregnancy, but in UC 35% vs 18% did
- Flares occurred in 1,2 trimester and immediate post partum
- RR 2.19 (1.25-3.97) for flare in UC

Effect of Crohn’s on Pregnancy

- Population based prevalence study from Sweden and Denmark
- 2377 women with CD vs. 869,202 without CD
- No increased risk for congenital abnormalities noted
- Risk for birth outcomes higher with h/o maternal surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mod preterm</td>
<td>1.76</td>
<td>1.51-2.05</td>
</tr>
<tr>
<td>Very preterm</td>
<td>1.86</td>
<td>1.38-2.52</td>
</tr>
<tr>
<td>SGA</td>
<td>1.22</td>
<td>1.00-1.49</td>
</tr>
<tr>
<td>C-section</td>
<td>1.93</td>
<td>1.76-2.12</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0.73</td>
<td>0.30-1.76</td>
</tr>
<tr>
<td>Con Abnl</td>
<td>1.01</td>
<td>0.79-1.29</td>
</tr>
</tbody>
</table>

Effect of UC on Pregnancy

• Northern European prevalence study
• Maternal UC associated with:
  – Preterm birth 1.77 (1.54-2.05)
  – Very preterm birth 1.41 (1.02-1.96)
  – C section 2.10 (1.84-2.19)
  – SGA 1.27 (1.05-1.54)
  – Congenital Ab 1.05 (0.84-1.31)
• Adverse birth outcomes associated with maternal disease activity

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</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>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)

Effect of Elevated CRP on Pregnancy Outcomes

- 8000 women being followed as part of Generation R Study—outcomes in women in Rotterdam
- CRP measured in early pregnancy in 6016 women, fetal growth in each trimester and neonatal outcomes studied
- Elevated CRP > 25 mg/L was associated with lower fetal weight in 3rd trimester, lower birth weight and SGA (2.94 [1.61-5.36])

Effect of IBD on Birth Outcomes

• Kaiser database 2000-12
• Outcomes both UC and CD (N = 512)
  – SGA 1.46 (1.14-1.88)
• Outcomes for UC only (N = 384)
  – Preterm birth 1.32 (1.00-1.76)
  – PROM 1.95 (1.26-3.02)
  – Ischemic placental disease 1.32 (1.03-1.69)
• Able to account for medication use

Major Congenital Anomalies in Women with IBD

- National mother-child database in UK
- All pregnancies with IBD and info on 5-ASA, thiopurine, steroid use 1990-2010
- Proportions of women taking each during preg
- 1703 vs 384,811 children born to mothers without IBD compared
- 2.7% vs 2.8% overall

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CA</td>
<td>0.98</td>
<td>0.73-1.31</td>
</tr>
<tr>
<td>5-ASA</td>
<td>0.82</td>
<td>0.42-1.61</td>
</tr>
<tr>
<td>CS</td>
<td>0.48</td>
<td>0.15-1.5</td>
</tr>
<tr>
<td>TP</td>
<td>1.27</td>
<td>0.48-3.39</td>
</tr>
</tbody>
</table>

Ban L. *Gastroenterol* 2014; 146:76-84.
Safety of Colonoscopy in IBD

- Case control of pregnant IBD patients matched to age, meds and disease activity
- 42 women underwent 47 lower GI procedures 2008-2014
- Median birthweight lower in cases but no difference in SA, gestational age, birth defects or APGAR scores

Drug Labeling for Pregnancy and Lactation


• Comments on Draft Guidance could be sent to FDA within 60 days of publication in Federal Register (Feb 2, 2015)

• Date of Implementation of final rule: June 30 2015
## Mesalamines and DBP

<table>
<thead>
<tr>
<th></th>
<th>ASACOL 400 mg</th>
<th>ASACOL HD 800 mg</th>
<th>DELZICOL 400mg</th>
<th>Pentasa</th>
<th>Apriso</th>
<th>Lialda</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>

*Has NOT been reformulated*
Medications: Mesalamine

- Meta-analysis of 7 studies
- 642 received 5-ASAs, 1158 did not

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</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>SA</td>
<td>1.14</td>
<td>0.65-2.01</td>
</tr>
<tr>
<td>Preterm</td>
<td>1.35</td>
<td>0.85-2.13</td>
</tr>
</tbody>
</table>

Corticosteroid Use during Pregnancy and Risk of Orofacial Clefts

- No statistically significant increased risk of orofacial clefts associated with the use of corticosteroids:
  - Cleft lip with or without cleft palate, (OR) 1.05 [0.80–1.38]; cleft palate alone, OR 1.23 [0.83–1.82]
- OR for cleft lip with or without cleft palate associated with the use of dermatologic corticosteroids was 1.45 (95% CI 1.03–2.05)

Hviid et al *CMAJ*. 2011 April 19; 183(7): 796–804
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>Infections</td>
</tr>
<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>• 4 cleft palates reported in non-steroid group only</td>
</tr>
<tr>
<td>Developmental delay</td>
</tr>
</tbody>
</table>
Long term Follow up Following in utero Exposure to Thiopurines

- Dutch prospective cohort
- 30 children exposed vs 340 not exposed
- No difference in global medical or psychosocial scores between groups
- No increased rate of infection or immunodeficiency noted
- Conclusion: TP use during pregnancy did not affect long term development up to 6 years of age

Intrauterine Exposure to Thiopurines

- 6TGN, 6MMP levels determined before, during and after pregnancy in mothers, cord blood for infants
- In 30 pts, median 6TGN decreased over time while 6MMP increased
- Fetal 6TGN concentrations correlated with maternal levels, no 6MMP detected
- 60% children had anemia at birth

Thiopurines and Congenital Malformations: Meta-Analysis

**Maternal**

Forrest Plot for Maternal Thiopurine Exposure and Congenital Anomalies (all studies)

- Francella: Odds Ratio, 95% CI
  - 0.8 (0.1, 7.8)
- Norgard: 2.9 (0.9, 8.9)
- Cleary: 1.4 (0.99, 2.2)
- Coelho: 0.6 (0.1, 3.3)
- Shim: 4.05 (0.24, 67.99)
- Combined: 1.45 (0.99, 2.13)

Test for heterogeneity: $Q = 3.315$, df = 4 (p value = 0.506), $I^2 = 0$

**Paternal**

Forrest Plot for Paternal Thiopurine Exposure and Congenital Anomalies

- Francella: Risk ratio (95% CI)
  - 0.63 (0.08, 5.24)
- Rajakpse: 45.71 (2.31, 905.26)
- Teruel: 0.91 (0.09, 9.80)
- Overall (95% CI): 1.87 (0.67, 5.25)

Test of heterogeneity: $\chi^2 = 5.76$, df = 2 (p-value 0.056)

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Outcome of Pancreatitis in Pregnancy

- Retrospective study of all singleton pregnancies in California from 2005-08 diagnosed with pancreatitis
- 342 identified, etiology not specified
- Pancreatitis associated with:
  - Preeclampsia OR 4.2 (2.99-5.93)
  - Preterm delivery OR 3.31 (1.93-5.56)
  - IU Fetal demise OR 4.35 (1.8-10.55)
  - SGA OR 2.26 (1.64-3.11)

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\(^1\) with the majority of transfer occurring in the 3rd trimester

- IgG transferred via the placenta persists longer in the newborn than the mother
  - Half-life of IgG in newborns is twice as long as the mother at 48.4 days\(^2\)

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>Patients, N</th>
<th>IFX</th>
<th>ADA</th>
<th>CZP</th>
</tr>
</thead>
<tbody>
<tr>
<td></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>

Anti-TNF Use and Pregnancy Outcomes

• GETAID population 133 pregnancies with TNF exposure vs 99 without
• 117 completed pregnancies total
• No difference in pregnancy or neonatal outcomes based on anti-TNF use
• Pregnancy complication associated with maternal smoking, B2 phenotype, flare during pregnancy, previous complicated pregnancy history

Seirafi M. *Aliment Pharmacol Thera* 2014; 40:363-373.
Pregnancy Outcomes after TNF Exposure

- 83 exposed pregnancies followed and compared with 86 disease matched non exposed pregnancies.
- 35 IFX, 25 etanercept, 23 ADA
- Rate of congenital anomalies not different for any anti-TNF exposure or controls
- No VATER/VACTERL cases

Diav-Citrin O. Reprod Toxicology 2014; 43:78-84.
Birth Defect Rate Low with Exposure to Anti-TNF Agents

- Live births from Danish and Swedish population-based health records
- Prevalence of birth defects in children both to mothers with chronic inflammatory conditions with or without anti-TNF exposure and HC
- 4.8% rate in diseased women vs 4.2% HC
- Odds ratio:
  - any defect anti-TNF exposure 1.32 (0.93-1.82)
  - CV defect 1.60 (0.93-2.58)
  - Urinary defect 2.22 (0.86-4.71)

Safety of Stopping Anti-TNF in Second Trimester

- 32 pts stopped therapy before week 25 compared with 22 treated until week 30
- 8/32 pts were on concomitant therapy
- 2/32 relapsed, 1/22 control group, $p = 1.00$
- No significant differences in birth weight, gestational age, congenital anomalies or APGAR scores between groups
- If mother *in remission*, safe to stop week 20

Recommendations:

• Pregnant women with IBD who are NOT in sustained remission should continue biologic through pregnancy

• **My practice:**
  • **Infliximab**: week 30-32 gestation
  • **Adalimumab/Golimumab**: week 36-38
  • **Certolizumab**: on schedule through pregnancy
  • **Vedolizumab**: week 30-32 gestation
Safety of Anti-TNF: Review

- Use of IFX, ADA before week 30 leads to fetal exposure
- Recommend cessation around week 20-22 if mother is in remission
- CTZ does not have to be stopped
- Since miniscule amounts seen in breast milk therefore while unlikely deleterious events cannot be excluded

Case 3: Management in Pregnancy

• 34 yo executive presents in first trimester of pregnancy with a severe flare of ulcerative colitis

• She was initially diagnosed with UC during her first pregnancy 2 years ago. She required mesalamine and prednisone and was in remission after pregnancy so stopped all her meds (2 years off meds, last time she saw you)
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
Herbal Therapies and Nursing

• Fenugeek is an herbal supplement used by Asian-Indian women for centuries to increase milk production
• Popular with certain lactation experts
• Causes rectal bleeding—mechanism thought to be related to its warfarin-like components
Very Low Levels of Biologics Are Detected in Breast Milk, But Do Not Adversely Affect Infant Outcomes: PIANO Registry

Methods
- 1-year post-partum follow-up (N=787 women)
  - 75% breastfed

Results
- Disease activity and immunomodulator use, but not biologic use, inversely associated with likelihood of breast feeding

<table>
<thead>
<tr>
<th>Biologic</th>
<th>N Detectable in Breast Milk (%)</th>
<th>Peak Time After Infusion (hr)</th>
<th>Range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>18/27 (67)</td>
<td>24-96</td>
<td>0–0.680</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>2/15 (13)</td>
<td>12-24</td>
<td>0–0.710</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>3/10 (30)</td>
<td>12-48</td>
<td>0–0.29</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>1/3 (33)</td>
<td>24</td>
<td>0–1.57</td>
</tr>
<tr>
<td>Golimumab</td>
<td>0/1 (0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>0/1 (0)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Breastfeeding while on biologics does not inversely affect infant growth, developmental milestones and infection rate

Matro R et al. Presented at DDW; May 18, 2015 Abstract 747.
Mode of Delivery

• Does mode of delivery matter?
• Systematic review of 7 studies
  – IBD in CS group 0.29%
  – IBD in vaginal delivery group 0.32%
  – OR 1.00 (0.75-1.33)
• Meta analysis of just case control studies did reveal OR 1.17 (1.03-1.32)

Bruce A. Inflamm Bowel Dis 2014; 20:1217-1226.
Impact of Mode of Delivery

• Study from BW and MGH in Boston
• 11 VD vs 50 CS vs 61 non-pregnant controls with p/a disease
• 3 had active p/a disease during pregnancy
• 1/3 CS done for obstetric reasons
• No difference in flares of p/a disease among delivered vs non-pregnant patients, and mode of delivery also not a factor

C-section and Risk of IBD

- Nationwide Danish Patient Registry
- 8142 dx IBD in 32.6 million person-yrs follow-up
- IBD at age 0-14 RR 1.29 (1.11-1.49) regardless of parental history
- Estimated 3.2% of cases before age 15 attributable to C-section

Pregnancy Outcome after Paternal Exposure to Thiopurine

<table>
<thead>
<tr>
<th></th>
<th>Paternal AZA/6-MP exposed (N=115)</th>
<th>Controls</th>
<th>OR (95%-CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All birth defects</td>
<td>11% (11/100)</td>
<td>7.7% (25/323)</td>
<td>1.47 (0.63–3.25)</td>
<td>0.31</td>
</tr>
<tr>
<td>Major Birth defects</td>
<td>3% (3/100)</td>
<td>2.2% (7/320)</td>
<td>1.38 (0.23–6.2)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Hoeltzenbein et al *Reproductive Toxicology* 34 (2012) 364–369
Summary

• We teach all our patients the importance of compliance with biologic therapy
  – Risk of antibody formation
  – Risk of attenuated response

• Pregnant women should not be different
  – No increase in the risk of birth defects
  – No increase in infections in newborns
  – Clear risk of increased adverse events with increased disease activity.
    • Postpartum is important too!
The placenta is the center of the chronic disease universe

Kent L. Thornburg, PhD; Nicole Marshall, MD
Final Thought

“If you don’t know where you are going, when you get there you’ll be lost”

- Yogi Berra