Case

- 23-year-old female, non-smoker
- Crohn’s ileocolitis diagnosed 3 years ago at college:
  - **SBFT**: 25 cm of inflammatory distal TI disease, no stricture
  - **Colonoscopy**: ulcerations in ileum, cecum, and right colon. Normal elsewhere.
  - No perianal disease!
- Responded to prednisone; switched to budesonide —CIR, subsequently could not maintain remission with 5-ASA 4.8g.
You discuss…

- Thiopurines* (azathioprine, 6-mercaptopurine)
- Methotrexate*
- Anti-TNF antibodies:
  - Infliximab
  - Adalimumab
  - Certolizumab
- Anti-Integrin antibodies:
  - Natalizumab
  - Vedolizumab

* Agents do not currently have FDA-indication for Crohn’s Disease

And then she mentions…..

- Getting married next month.
- She wants to start having a family in next 12-24 months
- She has a lot of concerns about being on mediation when she does get pregnant
- Accompanied by her husband
Thiopurines: IBD Birth Outcomes

- 64 pregnancies exposed 30 days prior to conception, 65 during entire pregnancy compared to pregnancies not exposed

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Ab</td>
<td>1.1</td>
<td>0.5-2.4</td>
</tr>
<tr>
<td>Induced preterm</td>
<td>4.0</td>
<td>1.5-10.8</td>
</tr>
<tr>
<td>LBW</td>
<td>1.7</td>
<td>0.3-8.7</td>
</tr>
<tr>
<td>Congenital abnl</td>
<td>1.1</td>
<td>0.5-2.9</td>
</tr>
</tbody>
</table>


Pregnancy Outcomes: CESAME Study

- 215 pregnancies (204 women) in the CESAME cohort 3/04 -12/07

- 3 exposure groups compared:
  1. "TP": Thiopurines (alone or associated with another treatment: 5-ASA, CS or anti-TNF)
  2. "Other": A drug other than a thiopurine
  3. "None": No medication

Pregnancy Outcomes: CESAME Study

“p” value = NS for all comparisons

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TP (n=86)</th>
<th>Others (n=84)</th>
<th>None (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Births (n)</td>
<td>64%</td>
<td>66.6%</td>
<td>60%</td>
</tr>
<tr>
<td>Prematurity (n,%)*</td>
<td>21.8%</td>
<td>16.0%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Low birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>under 2500g (n,%)*</td>
<td>15.8%</td>
<td>13.8%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Congenital abnormalities (n,%)*</td>
<td>2 (3.6%)</td>
<td>4 (7.1%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Conclusions

1. Thiopurine use is **not associated** with increased risk of congenital abnormalities.
2. Increased incidence of LBW and prematurity under TP was not significant and may correlate to the underlying disease.


Thiopurines: Birth Outcomes Meta-analysis

Summary

Thiopurine exposure associated with
• preterm birth

But not:
• Low birth rate
• Congenital abnormalities

Akbari et al Inflamm Bowel Dis 2013;19:15–22
Spanish Working Group in Crohn’s and Colitis

- 187 Pregnancies, retrospective
- Grouped by exposure 3 months prior / during pregnancy:
  - not exposed
  - A: thiopurine
  - B: anti-TNF
- “Unfavorable Global Pregnancy Outcome (GPO)”
  - Spontaneous / elective abortion; pregnancy ended before 37w; obstetrical complications; newborn LBW, ICU, congenital malform., death


<table>
<thead>
<tr>
<th></th>
<th>Unexposed</th>
<th>Thiopurine</th>
<th>Anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>318</td>
<td>187</td>
<td>66</td>
</tr>
<tr>
<td>Unfavorable GPO</td>
<td>31.8%</td>
<td>21.9%</td>
<td>34.8%</td>
</tr>
<tr>
<td>Pregnancy Complications</td>
<td>27.7%</td>
<td>20.9%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Neonatal Complications</td>
<td>23.3%</td>
<td>13.9%*</td>
<td>21.2%</td>
</tr>
</tbody>
</table>

P<0.01 vs. unexposed

Multivariate Analysis:
- Predictor of favorable GPO: thiopurines (OR 0.06; 95% CI 0.4-0.9, p<0.02)
- Predictor of unfavorable GPO: maternal age >35

Long-Term Follow-up: in-utero
Thiopurine Exposure

- 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

**Conclusion:**
Thiopurine use during pregnancy did not affect long term development up to 6 years of age


What About The Biologics?
Cytokines in Pregnancy

• Early: dominant proinflammatory profile
  – Embryo invades and damages maternal uterus to implant
• Middle:
  – Decrease in proinflammatory cytokines. Mother, fetus, placenta in synchrony
• Late:
  – Increase in proinflammatory cytokines to activate parturition

Plasma TNF-α levels higher during early pregnancy in women with recurrent miscarriage


Fertility May Be Improved By Anti-TNF Therapy

• 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>

Placental Transfer: IgG Classes

Placental Transport of IgG Subtypes in Human


Infliximab Transfer to Newborn

Data courtesy of Dr. Uma Mahadevan

* cord blood not tested
** newborn levels measured at week 2 (pt2), month 2 (pt9), month 1 (pt10)

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**Placental Transfer Less For Certolizumab (CTZ)**

- 31 women on anti-TNF had drugs measured
- Cord blood, child blood monthly until clearance
- IFX, ADA (not CTZ) could be detected as long as 6 months after birth


<table>
<thead>
<tr>
<th>IFX</th>
<th>ADA</th>
<th>CTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

**Pregnancy Outcomes: Maternal Infliximab**

### Infliximab: Pregnancy Outcomes: TREAT Registry

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Other Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MATERNAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancies</td>
<td>162</td>
<td>81</td>
</tr>
<tr>
<td>Healthy Babies</td>
<td>53%</td>
<td>60%</td>
</tr>
<tr>
<td>Neonatal Problems</td>
<td>5.6%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td>9.3%</td>
<td>4.9%</td>
</tr>
<tr>
<td><strong>PATERNAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancies</td>
<td>37</td>
<td>12</td>
</tr>
<tr>
<td>Healthy Babies</td>
<td>86%</td>
<td>83%</td>
</tr>
<tr>
<td>Neonatal Problems</td>
<td>10.8%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td>2.7%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>


### Adalimumab: Pregnancy Outcomes: OTIS Registry

<table>
<thead>
<tr>
<th>Outcome (n=126)</th>
<th>Adalimumab Cohort (n=30)</th>
<th>Diseased Comparison (n=51)</th>
<th>Non-Diseased Comparison (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Delivery &lt;37 weeks-all live births</td>
<td>11.1%</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>Birth weights grams in full-term infants, mean (SD)</td>
<td>3290</td>
<td>3259</td>
<td>3532</td>
</tr>
<tr>
<td>Malformations – all live births</td>
<td>7.4% *</td>
<td>0%</td>
<td>5.4% ***</td>
</tr>
<tr>
<td>Malformations – all pregnancies</td>
<td>6.6%</td>
<td>2% **</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

| RA patients + ADA Exposure | RA patients No ADA | No RA No ADA |

*1 infant ectopic testis; 1 microcephaly; **1 “non-specific chromosomal problems (spontaneous abortion); ***1 VSD; 1 postaxial accessory digit
Biologic Use in Pregnancy: CCFA Piano Registry

- **Biologics Alone:**
  - Spontaneous abortion*
    - RR 2.56 (1.07-6.12)
    - UC RR 4.85 (1.48-15.9)
    - *Patients more likely to report early pregnancy?*
  - Cesarean section
    - RR 1.23 (1.02-1.48)
    - *Due to OB-GYN and/or GI Doctor Preference?*

- **Combination Therapy (Thiopurine + Biologic):**
  - Preterm birth RR 1.83 (1.01-3.31)
  - UC:
    - Any complication
    - Pre-term Birth
    - Low Birth Weight
    - NICU Stay

Mahadeavan U et al. DDW 2012: Abstract 865.

Biologic Use in Pregnancy: CCFA Piano Registry

**NO Association with:**

- Rate of congenital anomalies
- Infant height and weight
- Overall rates of infection controlled for preterm birth
- Developmental milestones at month 4,9,12

Mahadeavan U et al. DDW 2012: Abstract 865.
Updates from PIANO

Babies of IBD moms exposed in-utero to a thiopurine + anti-TNF (vs. babies of IBD moms not exposed)¹:
1. Better Developmental Milestones
2. Similar Rates of Congenital Abnormalities
3. Higher Rates of Pre-Term Birth
   a. UC: Also lower birth weight, need for NICU.

Exposure to anti-TNF in 3rd trimester²:
1. No higher rates of preterm birth
2. No higher rates of infections in 1st year of life
3. No higher rates of flares in T3 or first 4 months post-partum

Mahadevan U et al. Gastroenterology 2014;146(5):S-1 (abstract 1)

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Anti-TNF: Important Issues

• Should you stop therapy in 3rd Trimester?
  • Opinion of some experts: Yes to “minimize exposure”
  • Opinion of other experts: Not necessary, given safety data

• Babies born to mothers on adalimumab or infliximab should not get any live vaccines for the first 6 months of life:
  • USA: Do not give rotavirus vaccine prior to 6 months.
“What About Anti-Integrin Antibody Therapy…?”

Natalizumab in Pregnancy

- Not aware of fetal serum level studies in humans
- Cynomologus monkeys treated with 2.3-fold clinical dose demonstrated:
  - Mild anemia
  - Reduced platelet count
  - Increased splenic weight
  - Reduced liver and thymus weight

Pregnancy Outcomes: Maternal Natalizumab: TPER Registry

- Prospective “Tysabri Pregnancy Exposure Registry
- 2/2013: 375 pts (7 with Crohn’s)
- 362 pregnancies; 11 ongoing, 10 lost to followup.
  - 314 live births: 8 twin, 13 elective terminations, 34 spontaneous abortions, 1 stillbirth
  - “Major and minor birth defects in 28 pregnancy outcomes (26 mothers)
  - “rates similar to expected”
  - Note: All authors are employees of Biogen Idec.


Vedolizumab in Pregnancy

<table>
<thead>
<tr>
<th>Pregnancy Outcome</th>
<th>Treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=3)</td>
<td>Total (n=27)</td>
</tr>
<tr>
<td>Pregnant Patients/Volunteers</td>
<td>Healthy</td>
<td>UC</td>
</tr>
<tr>
<td>Live birth</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Elective termination</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Undocumented†</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| Pregnant Partners               | Treatment                      | Total (n=20) |
|                                 | Placebo (n=4)                 | Total (n=18) |
| Placebo (n=4)                   | Healthy| UC | CD | Healthy| UC | CD | |
| Live birth                      | 0 | 2 | 1 | 0 | 6 | 3 | 12 |
| Elective termination            | 0 | 0 | 1 | 0 | 1 | 1 | 3 |
| Spontaneous abortion            | 0 | 0 | 0 | 0 | 1 | 1 | 2 |
| Undocumented†                   | 0 | 0 | 0 | 0 | 1 | 2 | 3 |

Abbreviations: CD, Crohn’s disease; UC, ulcerative colitis.
† Includes pregnancies that were ongoing at last patient contact and pregnant partners who withdrew consent.
Includes studies NCT01981619, C13001, NCT00619489, NCT00783718 [GEMINI 1], NCT00978588 [GEMINI 2], and NCT00766633 [GEMINI LTS: data up to 27 June 2013].
She agrees to start an anti-TNF agent…

- Quickly goes into remission
- Able to wean quickly off steroids
- Gets pregnant later that year.
- Has healthy full-term baby!!

Summary

- Thiopurines: safety data seems to belie the FDA safety rating.
- Methotrexate: forbidden
- Anti-TNF agents: data supports usage
  - Certolizumab doesn’t cross placenta, but has less safety data.
  - Anti-integrin antibodies:
    - Natalizumab: data supports usage
    - Vedolizumab: data anticipated