Fertility and Pregnancy in IBD

Uma Mahadevan-Velayos MD
Associate Professor of Medicine
UCSF Center for Colitis and Crohn’s Disease
Higher Incidence of Abnormal Pap Smears in Women With IBD

- 40 pts with 134 paps vs. 320 controls paps
  - Abnormal pap with IBD OR = 4.3 (2.2-10.5)
  - Higher risk abnormalities OR = 3.1 (1.3-8.7)
  - Immunomodulators: OR = 4.5 (1.5-12.3)
  - Imm: exp vs. non-exp: OR 1.9 (1.1, 12.1)

Conclusions:
- Women with IBD
  - Higher risk of an abnormal Pap smear vs. healthy controls.
- Immunomodulator use
  - Higher risk of an abnormal Pap smear associated with HPV
- Women with IBD meet ACOG guidelines for increased cancer screening
- HPV vaccine in young patients

Kane S, AJG 2007;102L1-6
Fertility

• With both UC and CD, the risk of fertility prior to surgery appears to be similar to the general population
  – Infertility in NE Scotland population based study
    • 15% UC (n= 138) vs. 14% general population
    • 14% CD (n= 177) vs. 14% general population
      – Surgical therapy:20% Medical therapy: 8%
  • Olsen: 290 women with UC with IPAA
    – After diagnosis of UC: FR = 1.01
    – After surgery IPAA: FR*= 0 .20

IPAA: Cumulative Incidence of Pregnancy Within 5 Years

Cumulative Incidence of Pregnancy

Time to Pregnancy (months)

Before diagnosis
Reference
Before surgery
After surgery

# Pregnancy Outcomes:
## Population Based Studies

<table>
<thead>
<tr>
<th></th>
<th>IBD</th>
<th>UC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Birth</td>
<td>✗</td>
<td>✗</td>
<td>✗ ✗</td>
</tr>
<tr>
<td>LBW</td>
<td>✗</td>
<td></td>
<td>✗ ✗</td>
</tr>
<tr>
<td>SGA</td>
<td></td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>Congenital Malformation</td>
<td></td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>Caesarean Section</td>
<td></td>
<td>✗</td>
<td></td>
</tr>
</tbody>
</table>

Kornfeld: Am J Obstet Gynecol 1997 (n=756 IBD)
Fonager: Am J Gastroenterol 1998 (n=510 CD)
Norgard: Am J Gastroenterol 2000 (n=1531 UC)
Domitz: Am J Gastroenterol 2002 (n=107 UC, 155 CD)
Meta-Analysis

- 12 studies
  - N= 3907 (CD 1952, UC 1113) vs. 320, 531
- Prematurity OR = 1.87 (1.52-2.31) p<0.001
- LBW OR = 2.10 (1.38-3.19) , p<0.001
- C-section OR = 1.50 (1.26-1.79) p <0.001
- Congen Abnorm. = 2.37 (1.47-3.82) p <0.001
  - 4 studies reported on the incidence IBD vs. controls, no difference
  - UC vs. controls in two studies (Larzilliere 1998, Dominitz)
## Dominitz (2002)

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>UC (107)</th>
<th>CD (155)</th>
<th>Controls (1308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm delivery</td>
<td>10.4%</td>
<td>15.2%* p&lt;0.005</td>
<td>7.2%</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>7.6%</td>
<td>16.8%* p&lt;0.001</td>
<td>5.3%</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>10.5%</td>
<td>15.2%* p&lt;0.001</td>
<td>6.9%</td>
</tr>
<tr>
<td>Congenital (n) Malformation</td>
<td>7.9%* (8) p&lt;0.001</td>
<td>3.4% (5)</td>
<td>1.7% (21)</td>
</tr>
</tbody>
</table>

**CD**: hyrdocele (2), penile anomaly, GI malform (pilonidal cyst) hearing loss

**UC**: undescended testicle, obstruction pelvis/ureter, multiple (death)-chromosomal, CV, resp; Subluxation hip, syndactyly toes, omphalocele (death)
Outcomes: Ulcerative Colitis

- Norgard (AJG 2003)
  - Hungarian Case Control Surveillance of congenital anomalies (CA): 1980-1996
  - UC: 71 cases (.3%): 95 controls(.2%)
  - OR: 1.3 (95%CI=0.9-1.8) [Adjusted for parity, age, SAS/other drugs]
    - Limb deficiencies: OR=6.2 (2.9-13.1)
    - Obstructive urinary CA: OR=3.3 (1.1-9.5)
    - Multiple CA: OR=2.6 (1.3-5.4)
<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>493</td>
<td>461</td>
<td></td>
</tr>
<tr>
<td>Mean Age at Conception (yrs)</td>
<td>30 [6.0]</td>
<td>30 [5.8]</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smoked</td>
<td>18.5%</td>
<td>16.9%</td>
<td>0.52</td>
</tr>
<tr>
<td>IBD type</td>
<td>--</td>
<td>CD: 154</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>UC: 300</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indeterminate: 7</td>
<td></td>
</tr>
<tr>
<td>Median IBD Duration (yrs)</td>
<td>--</td>
<td>4.2 [5.6]</td>
<td></td>
</tr>
<tr>
<td>Any Immunosuppess</td>
<td>2 (0.6%)</td>
<td>19 (4%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Any Salicylates</td>
<td>1 (0.3%)</td>
<td>234 (51%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Any Steroid Use</td>
<td>0</td>
<td>96 (21%)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Mahadevan U Gastroenterol 2007 Oct;133(4):1106-12
### Results

<table>
<thead>
<tr>
<th>Adverse Outcomes</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conception</td>
<td>1.65</td>
<td>1.09-2.48</td>
</tr>
<tr>
<td>Pregnancy Outcomes</td>
<td>1.54</td>
<td>1.00-2.38</td>
</tr>
<tr>
<td>Pregnancy Complications</td>
<td>1.78</td>
<td>1.13-2.81</td>
</tr>
<tr>
<td>Newborn Outcomes</td>
<td>1.89</td>
<td>0.98-3.69</td>
</tr>
</tbody>
</table>

*Controlled for maternal age, current ETOH, current tobacco, Caucasian ethnicity, number of prenatal visits (except conception)
## Pregnancy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live Birth</strong></td>
<td>308 (68.3%)</td>
<td>274 (60%)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>SAB</strong></td>
<td>60 (14%)</td>
<td>79 (17%)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>LBW</strong></td>
<td>11 (3.6%)</td>
<td>20 (7.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Preterm Birth</strong></td>
<td>28 (9.6%)</td>
<td>36 (14.2%)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Congenital Anomalies</strong></td>
<td>30 (6%)</td>
<td>34 (7%)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Cesarean Section</strong></td>
<td>37 (9.5%)</td>
<td>61 (13.8%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Predictors: IBD, surgery for IBD, non-Caucasian
Medication use and disease severity were not predictors

*Mahadevan Gastro 2007*
Predictors of Poor Outcome

• IBD
  – OR 2.18 (1.8-3.0) [Mahadevan 2005]
• Active Disease (UC and CD)
  – Not predictive
    • Mod-high active disease OR .89 (0.46-1.73) [Mahadevan]
    – Predictive
      • Conception => Fetal loss [Morales 2000] (n=35)
      • Pregnancy => LBW, Preterm [Bush 2004] (n =116)
• Ileal Crohn’s Disease
  – (p=.035) [Moser 2000] (n = 65)
• Previous bowel resection
  – (p=.065) Moser
    – OR 5.8 (1.74-19.45) [Mahadevan]
**Disease Activity During Pregnancy in Women with IBD**

- **Exposure:** IBD disease activity during conception, each trimester and the postpartum period (1 month)
  - Inactive, mild, moderate, severe

![Chart showing disease activity in Crohn's disease and ulcerative colitis across trimesters and postpartum period.](chart)

Medical Therapy in Conception and Pregnancy
Pregnancy Category

- **Category A**: Controlled studies show no risk
- **Category B**: No evidence of risk in humans
- **Category C**:
  - Animal reproduction studies show adverse effect
  - No adequate studies in humans
  - Drug’s benefits in pregnant women may be acceptable despite its potential risk
- **Category D**: Positive Evidence of Risk
- **Category X**: Contraindicated in Pregnancy
Fish Oil

- Essential Fatty acids (EFA) and Docosahexaenoic acid (DHA)
  - Potential antithrombotic effect
  - Prolong gestation
  - No evidence of prevention of proteinuric pregnancy
- Mild benefit in Crohn’s disease

Aminosalicylates (B,C)

- Meta-analysis 7 studies: 642 5ASA, 1158 no med
  - Congenital anomalies: OR 1.16 (0.76, 1.77)
  - Stillbirth OR 2.38 (0.65, 8.72)
  - SAB OR 1.14 (0.65, 2.01)
  - Preterm delivery 1.35 (0.85, 2.13)
  - LBW OR 0.93 (0.46, 1.85)
- Sulfasalazine given w/ folic acid 1 mg BID
  - Folic acid: neural tube defects, CV, GU, cleft palate
  - Case reports of congenital malformation
- Placental and Breast Transfer Occurs
  - Potential allergic reaction newborn: watery diarrhea
  - SAS not associated with kernicterus or displacement of bilirubin from albumin
- Olsalazine: Pregnancy category C. All others, B

Rahimi Reprod Toxicol 2008
Corticosteroids (C)

- Case-control study in 1st T
  - Increased risk of oral clefts
  - Overall risk of malformations low
  - In transplant setting:
    - Adrenal suppression in newborn
    - Premature rupture of membranes
- Compatible with breast feeding
- Entecort (budesonide)
  - Orally inhaled budesonide not associated with increase risk of fetal abnormalities
Antibiotics

• Metronidazole (B) / Ciprofloxacin (C)
  – Low risk of teratogenicity
    • Metronidazole: prospective controlled study, 2 meta-analysis
      – However, 2nd, 3rd T use, 1st T cleft lip, palate
    • Ciprofloxacin: prospective controlled study low risk of defects
      – Affinity for bones, arthropathy in children
  – Breast feeding not advised on MNZL, probably compatible with ciprofloxacin
  – Minimal benefit in CD and UC with longer use-avoid

• Rifaximin: Pregnancy C
  – Teratogenicity in animal studies
  – Safety in humans in pregnancy/breastfeeding unknown
6MP/AZA (D)

- Teratogenic in animals (mice, rabbits, rats)
  - Given IV/IP at supratherapeutic doses. (low oral bioavailability: 47% AZA, 16% 6MP)
  - Increased cleft palate, ocular, skeletal, urogenital anomalies, hydrocephalus
  - Poor oral bioavailability may produce levels too low to have substantial teratogenic effect
- Fetal liver in early pregnancy lacks inosinate pyrophosphorylase to convert AZA to active metabolites

Polifka and Friedman (Teratology 65:240-261. 2002)
Human Studies: 6MP/AZA

- Transplantation Experience
  - Frequency of CA in renal tx 0.0-11.8% in 27 clinical series
  - No recurrent pattern of anomalies seen
  - No increase in anomalies in NTPR (Armenti 1994) in kidney transplant
- No CA in rheumatic disease, SLE
- Experience in IBD
  - Alstead (1990): 14 pts: 7 entire pregnancy: no CA
  - Francella (2003): Retrospective
    - 79F(24 UC), 76M(27 UC). 325 pregnancies
    - No difference in outcomes with 6mp exposure
    - Only 15 patients on 6mp throughout pregnancy
Azathioprine/6MP

- Population based prescription registry, Denmark
  - 9 pregnancies (30d before concept/1st trimester)
  - 10 pregnancies (exposed entire pregnancy)
  - Outcomes vs. (1) 19,418 pregnancies no drugs (2) any drug (3) 6MP/AZA >3 mos before pregnancy
- 11 pts: 55% IBD, 45% other disease
  - Congenital malform OR= 6.7 (95%CI 1.4-32.4)
  - Mortality OR = 20 (2.5-161.4)
  - Preterm Birth OR = 6.6 (1.7-25.9)
  - LBW OR = 3.8 (0.4-33.3)
- After exclusion of most ill pt (AIH), no statistical significance in OR.

Danish Cohort Study

- Danish cohort study of 900 children born to CD women (1996-2004) based on the National Registry of Patients, the Birth Registry, and nationwide prescription database.
  - Pregnancies were classified according to receipt of prescriptions for CD medication: no drugs (reference group), 5-ASA/sulfasalazine, steroids, and azathioprine (AZA)/6-mercaptopurine (6-MP).
  - Proxy measure for disease activity.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AZA</th>
<th>Steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preterm Birth</strong></td>
<td>25%</td>
<td>12.3%</td>
<td></td>
</tr>
<tr>
<td>(6.5%)</td>
<td>RR = 4.2</td>
<td>[1.4, 12.5]</td>
<td>[0.6, 3.3]</td>
</tr>
<tr>
<td><strong>CA</strong></td>
<td>15.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5.7%)</td>
<td>RR = 2.9</td>
<td>(0.9, 8.9)</td>
<td></td>
</tr>
</tbody>
</table>

Norgard AJG 2007 July 102 (7)
Azathioprine and Teratogenicity

- 189 pregnant women on AZA who contacted one of seven teratogen information services were compared to a cohort of 230 pregnant women who took non-teratogenic treatments.
- Rate of major malformations did not differ with six neonates each:
  - AZA (3.5%) vs control (3.0%) (p = .775; OR 1.17; CI: 0.37, 3.69).
- Mean birth weight and gestational age were lower in AZA group:
  - 2,995g vs. 3,252g [p = .001]
  - 37.8 weeks vs. 39.1 weeks [p = .001]
- The AZA group had more prematurity
  - 21.4% vs. 5.2% [p < .001]
- The AZA group had more low birth weight
  - 23% vs. 6.0% [p < .001]

Breastfeeding on AZA/6MP

- AZA/metabolites do cross placenta; 6TGN is found in infant at a slightly lower levels
- Three studies on breastfeeding:
  - Sau: 31 samples/10 women (AZA 75-150 mg)
    - 1 patient had low levels in breast milk
    - 6mp and 6tgn undetectable in neonatal blood
  - Gardiner: 4 women aza 1.2-2.1 mg/kg/d
    - 6TGN and 6MMPn not found in infant
  - Moretti: 4 women aza
    - Levels of 6mp undetectable by HPLC

Cyclosporine/ Tacrolimus (C)

- **Cyclosporine**
  - Meta-analysis of 15 studies (14 pts) OR malformations 3.83 (0.75-19.6)
  - IBD: one case administered at 29 weeks. Healthy fetus at 34 weeks
  - In fulminant colitis, better than emergent colectomy
  - Breast feeding not advised: Csa secreted in breast milk

- **Tacrolimus**
  - Benefit over CSA, lower hypertension, hyperlipidemia in mother
  - Higher incidence of diabetes in newborn
  - 5.6% malformation rate in newborns, no specific pattern
  - Prematurity common
  - Breastfeeding not recommended
Infliximab (B) Safety Database in Pregnancy: Outcomes of Women Exposed to Infliximab During Pregnancy

Infliximab in Pregnancy

10 Crohn’s disease patients intentionally exposed to infliximab during pregnancy

- 8 women received maintenance infusions
- 2 women received initial infusions

10 Live Births

- Congenital malformations (N=0)
- IUGR (N=0)
- SGA (N=0)
- Preterm (N=3)
- LBW (N=1)

8 Caesarean sections: 2 active luminal, 3 perianal disease, 1 preterm

High Serum Infliximab Levels in Newborn of a Mother Treated During Pregnancy

<table>
<thead>
<tr>
<th>Infliximab infusion (10 mg/kg)</th>
<th>Time (weeks) from birth</th>
<th>Breast fed 7 wks</th>
<th>Breast feed resumed Wk 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>+</td>
<td>0</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>+</td>
<td>2</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>+</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Birth 41 wks

<table>
<thead>
<tr>
<th>Infliximab level</th>
<th>µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother serum</td>
<td>40</td>
</tr>
<tr>
<td>Baby serum</td>
<td>40</td>
</tr>
<tr>
<td>Breast milk</td>
<td>0</td>
</tr>
</tbody>
</table>

Immune studies at 6 months:
T and B lymphocytes normal
IgG, IgM and IgA levels normal

Six women completed pregnancy.
Four had Crohn's disease and 2 had UC
  - 2 were on concomitant azathioprine
  - Mean maternal age was 36 years (range 30-40)
  - Pts were on 5 mg/kg of infliximab
Mean infusion interval: 8 wks (4-12)
Mean time b/w birth and last INF infusion:
  - 66 days (2-120)
All patients were in remission at birth.
  - 3 flared within 5 months post-partum
<table>
<thead>
<tr>
<th>Pt #</th>
<th></th>
<th>1</th>
<th>2</th>
<th>3*</th>
<th>4*</th>
<th>5*</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Breastfed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Maternal INF level pre-birth</td>
<td></td>
<td>21.3</td>
<td>2.0</td>
<td>8.3</td>
<td>5.7</td>
<td>6.6</td>
<td>15.3</td>
</tr>
<tr>
<td>Days from last infusion to birth</td>
<td></td>
<td>30</td>
<td>2</td>
<td>90</td>
<td>90</td>
<td>120</td>
<td>49</td>
</tr>
<tr>
<td>Maternal INF level Birth (mcg/ml)</td>
<td></td>
<td>15.1</td>
<td>1.4</td>
<td>19.2</td>
<td>3.8</td>
<td>4.8</td>
<td>14.5</td>
</tr>
<tr>
<td>Cord Blood INF</td>
<td></td>
<td>--</td>
<td>2.0</td>
<td>26.5</td>
<td>3.3</td>
<td>8.8</td>
<td>20.5</td>
</tr>
<tr>
<td>Newborn INF at Birth</td>
<td></td>
<td>25.3</td>
<td>2.9</td>
<td>23.6</td>
<td>4.2</td>
<td>8.7</td>
<td>28.2</td>
</tr>
<tr>
<td>Month from birth INF undetectable</td>
<td></td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
• Three case reports of use in CD pregnancy
• OTIS (Organization for Teratology Information Specialists) reports 27 women enrolled in a prospective study of adalimumab in pregnancy and an additional 47 adalimumab exposed pregnant women in a registry
  – The rate of spontaneous abortion and stillbirth was similar to the diseased comparison and the general population. The rates of congenital malformation and preterm delivery are also within the expected range.
Biologics and Pregnancy

- Certolizumab: no published data in humans
- Natalizumab (C): IgG4, placental transfer in 1st trimester
- FDA Database: Anti-TNF’s
- 41 reported CA’s (12/2005):
  - 22 etanercept, 19 INF
  - 15 (37%) > 1 CA
  - Most common is cardiac defect
  - 1 VACTERL (ETN) Separate VACTERL in ADA
    - 24/41 (59%) had some component of VACTERL (11 INF)
    - 24/41 cases (59%) mother on no other meds
    - Vertebral, anal atresia, cardiac defect (VSD), tracheosophageal fistula with esoph atresia, renal, limb abnormality (radial dysplasia)
      - Associated with DM: Inhibition of cholesterol-dependent sonic-hedgehog morphogenetic pathway

Carter J ACR 2007 Abstract #667
Use with Caution

- Diphenoxylate (C): Teratogenic in animals
- Loperamide (B): ↑ CV defects in one study
- Bisphosphonates (C): Half life 10 years
  - animal studies: alendronate crosses placenta causes anatomic changes in fetal bone
  - 24 pregnancies, no increased teratogenic risk
- Methotrexate (X)
  - Known abortifacient
  - Teratogenic (skeletal defects, cleft palate)
- Thalidomide (X)
  - Birth defects

Special Circumstances: Perianal Crohn’s Disease

- Episiotomy may predispose to perineal disease (17.9%) without prior disease
  - 103 Vaginal delivery (87% episiotomy) [Brandt 95]
- Active perianal disease: Caesarean section
  - No history (1/39) or inactive (0/11) perianal disease at birth, risk of relapse very low
  - 4/4 with active perianal disease worsened post-vaginal delivery [Ilnyckyj 1999 AJG manitoba database]

Fulminant Ulcerative Colitis

- Indications for surgery in pregnant pt are same:
  - Fulminant refractory disease, hemorrhage, megacolon
- Case series in 70’s-80’s with high fetal mortality (40-50%)
- First trimester: turnbull-blowhole colostomy (colonic decompression and ileal diversion)
- Later pregnancy: synchronous delivery and colectomy may be best option
- Would attempt medical therapy first

Haq Int J Colorectal Dis 2005
Boulton AJG 1994
Pouch Function and Pregnancy

• Reversible deterioration of pouch function during pregnancy
• No long-term detriment to pouch function
• Mode of delivery determined by obstetric indications
  – Cesarean section to preserve sphincter
• Maybe less complications than Kock pouch or ileostomy
Summary: Women

- Fertility decreased with surgery
- Pregnancy Outcomes
  - Increased rates Preterm birth, SGA, LBW
  - No clear increase in congenital anomalies
- Medications
  - Yes: 5ASA, Steroids, 6MP/AZA, Infliximab, adalimumab
  - No: MTX, Thalidomide, Diphenoxylate
- Recommendations:
  - Control disease prior to conception
  - Continue most medications
  - High Risk Obstetrician