Improving treatment for women with Crohn’s and Ulcerative colitis

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Concerns

- Men are different from women
- Intimacy
- Contraception
- Cervical cancer
- Pregnancy and nursing
- Menopause
- Osteoporosis
Our patient

- 16 year old girl with cramping, bloody diarrhea due to ileocecal Crohn’s disease, perianal abscess
- On adalimumab and in remission, required steroids for 3 months
- Brother 9 years old and diagnosed with Crohn’s as well
**IBD: Systemic Complications**

- Eye inflammation*
- Lower bone density*
- Liver and bile duct inflammation
- Gallstones
- Skin lesions
- Kidney stones
- Subfertility*
- Ovaries
- Uterus
- Arthritis and joint pains
- Growth failure in children

*Higher incidence in women.

CROHN’S IS 1.8x MORE COMMON IN WOMEN
Menstrual periods

- May be **irregular** with active disease
- **Menstrual symptoms significantly higher** for IBD patients
- **IBD symptoms may worsen around menses**
  - Consider menstrual suppression (Depoprovera, Lupron)

Abnormal Pap smears

- Conflicting results, 18 vs 5% abnormal
- Higher rate of advanced results, associated with immune suppression
- Trend toward increased incidence of cervical Cancer in women with IBD
- May be affected by smoking and duration of birth control pills
Recommendations

- Consider gardasil vaccine
- Any patients on immunosuppression should consider annual pap smear
5 years later she meets the man of her dreams and gets married...
Sexual Development

- Body image is often a concern
- Children with IBD may have delayed puberty
- Different from peers
- Once puberty occurs, hormonal cycles are generally normal
Physical barriers

- Complications of IBD
  - Rectovaginal fistulas
  - Perianal disease in 20-80%
- Ostomy
- Post-surgical changes
  - Resection alters organ position causing painful intercourse
  - Pelvic nerves may be damaged decreasing sensation
Emotional barriers

- Medications
  - Steroids decrease libido
- Fear of incontinence and pain
- Fatigue/lack of energy
- Negative body image
  - Side effects of prednisone
  - Scars, ostomy
- Challenge to unstable relationships
Solutions

- Maximize treatment of colitis
- Empty ostomy prior; (my heart ties)
- Use enemas/suppositories after
- Lubrication
- Communication-support groups, counselors
  - Partner
  - Docs are poor at addressing sexuality

Borum, M. IBD. 16(2):181, 2010 Feb
Birth Control

- IUD
  - If someone has abdominal pain, don’t assume it is IBD

- Oral contraceptives-207 articles
  - Don’t cause flare
  - Don’t increase clots in IBD patients
  - No evidence for poor absorption

Zapata, L. Contraceptive use among women with IBD: A systematic review. Contraception. 82(1):72-85, 2010 Jul
They finish college, buy a house and build a crib...
Effect of IBD on Fertility

- Increased rate of voluntary childlessness
- Not affected by medications in women
- Fertility in patients with UC or inactive CD is unaffected\(^1\)
- Decreased ability to conceive after colectomy/pouch
- Fertility may be decreased in patients with active CD\(^1\)

It’s Positive!!
MOM

- IBD may increase the risk of blood clots (X6.1), anemia, and malnutrition (x20) during pregnancy
- Rule of thirds

Effect of Pregnancy on CD

Inactive Disease at Time of Conception

- No Relapse: 73%
- Relapse*: 27%

Active Disease at Time of Conception

- Worsened: 33%
- Continued: 32%
- Decreased: 34%

n=186
n=93

*Relapse rate is similar to non-pregnant CD patients in a year

Miller JP. J R Soc Med 1986;79:221-225
Pregnancy with IPAA for UC

- pouch-related complications infrequent
- ↑ stool frequency and incontinence during pregnancy
- 83% regained prepregnancy function
- Delivery method did not affect symptoms
- PREGNANCY IS SAFE

Treating MOM

- Laboratory studies
- Ultrasound and MRI – safe
- Low-dose X-rays pose minimal fetal risk\(^1\)
- Endoscopy – safe if used for appropriate indications\(^2\)
- Flexible sigmoidoscopy – safe\(^2\)
- Colonoscopy – should only be used for life-threatening colonic disease or when only alternative is laparotomy\(^2\)

Drugs in Pregnancy

- Pharmaceutical companies almost never test products in pregnant women
- *PDR®* disclaimer: use in pregnancy is not recommended unless benefits justify risk to fetus
- FDA classifications (A, B, C, D, X)
  - Ambiguous
  - Difficult to interpret and use in counseling

*PDR® = Physicians’ Desk Reference®; FDA = Food and Drug Administration.*
Pregnancy-Risk Categories

- **A**: Controlled human studies do not show risk to fetus; chance of risk remote
- **B**: No evidence of risk to fetus in human studies; chance of risk remote but possible
- **C**: Inadequate studies in humans; risk cannot be ruled out, but benefits may outweigh risks
- **D**: Positive evidence of fetal risk; benefits might outweigh risks in life-threatening situations when safer drugs are ineffective
- **X**: Contraindicated in pregnancy

# Pregnancy Categories of IBD Medications

<table>
<thead>
<tr>
<th>Category B</th>
<th>Category C</th>
<th>Category D</th>
<th>Category X</th>
</tr>
</thead>
<tbody>
<tr>
<td>mesalamine*</td>
<td>olsalazine*</td>
<td>azathioprine</td>
<td>methotrexate</td>
</tr>
<tr>
<td>balsalazide*</td>
<td>ciprofloxacin</td>
<td>6-mercaptopurine</td>
<td>thalidomide</td>
</tr>
<tr>
<td>sulfasalazine*</td>
<td>cyclosporine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>corticosteroids*+</td>
<td>diphenoxylate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab*+</td>
<td>tacrolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metronidazole+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>loperamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab+</td>
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</tbody>
</table>

*Indicated for UC
+ indicated for CD

PIANO
_Pregnancy in Inflammatory Bowel Disease And Neonatal Outcomes:
A National Prospective Registry

Uma Mahadevan-Velayos, Christopher Martin, Robert Sandler, Sunanda Kane, Marla Dubinsky, James Lewis, Sylvia Degli-Espositi, William Sandborn, Bruce Sands & CCFA Clinical Alliance
RESULTS

- 404 enrolled eligible women (5/29/2009)

- 237 pregnancies ended
  - Group 1: n = 106
    - 12 no medications
  - Group 2: n = 56
    - 1 CSA
  - Group 3: n = 75
    - 45 INF (1 MTX + INF)
    - 18 ADA
    - 2 INF + ADA
    - 3 CZP + ADA
Conclusions

In this prospective cohort registry of pregnant women with IBD an interim analysis demonstrates no increased risk of adverse events, including congenital anomalies, among patients exposed to AZA/6MP or anti-TNF agents.
Key points

- No significant increase in adverse outcomes/congenital abnormalities due to medications (other than MTX and thalidomide)
- Sulfasalazine Interferes with folic acid metabolism

Outcomes associated with IBD during pregnancy (may not be dependent on flare):

- Preterm delivery
- Low Birth weight
- Small for gestational age
- Miscarriage
- POSSIBLE-developmental delay
- *** more research needed

## Effects of IBD on Pregnancy: Results of 24 Published Reports

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pregnancies</td>
<td>1155</td>
<td>388</td>
</tr>
<tr>
<td>Normal birth</td>
<td>83%</td>
<td>83%</td>
</tr>
<tr>
<td>Congenital abnormality</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Therapeutic abortion</td>
<td>4.8%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Outcomes were similar to those in general population.

Adapted with permission from Fertility, sterility and pregnancy in chronic inflammatory bowel disease by Järnerot G. from Scand J Gastroenterol. www.tandf.no/gastro, 1982;17:1-4, by permission of Taylor & Francis AS.
Delivery

- Vaginal delivery is usually safe for women with inactive perianal symptoms\(^1\)
- However, vaginal delivery with episiotomy can be a risk factor for perineal complications\(^2\)
- CD- 17% flare following vaginal delivery
- 44% of women with IBD have cesarean sections

Recommendations for Pregnancy

- Minimum of 3 months quiescent disease prior to conception; see gastroenterologist at least once each trimester
- Control disease (continue medications)
- Maintain nutrition including 2g folate daily
- Monitoring of fetal growth particularly important—consider High risk obstetrician
<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommendations (80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>No human data: probably compatible</td>
</tr>
<tr>
<td>Azathioprine/6-mercaptotopurine</td>
<td>Human data limited, but suggest minimal transfer to the infant</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>No human data: potential diarrhea</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>No human data: risk unknown</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Limited human data: probably compatible</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Compatible</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Limited human data: potential toxicity</td>
</tr>
<tr>
<td>Fish oil supplements</td>
<td>No human data</td>
</tr>
<tr>
<td>Infliximab</td>
<td>No human data: probably compatible</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Limited human data: potential diarrhea</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Limited human data: potential toxicity</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>Limited human data: potential diarrhea</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Safety unknown</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Limited human data: potential diarrhea</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Limited human data: potential toxicity</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>No human data: potential toxicity</td>
</tr>
</tbody>
</table>
Breastfeeding

- Series of 15 babies fed with moms on AZA….at 4.7 years, no increase in infecti
- Does not increase risk for flare and may be protective

Childhood vaccinations

- No live vaccines (flu, mmr, varicella, rotavirus) for 1st 7-12 months if exposed to biologic
- Consider booster of tetanus and H influenza as needed
- Consider checking titers of vaccines
Inheritance

- IBD is multifactorial
- Genetic predisposition is not Mendelian
- Child has 5% risk of Crohn’s with affected parent
  - 1.6% risk with parent with UC
- Child has 37% risk if both parents have IBD
- Risk higher in Jewish families (7.8% vs 5.8%)
- 37% risk if identical twin has IBD
Time passes quickly...now she’s a grandmother....
Does menopause affect IBD?

- NO
- Rate of flare postmenopausal may be reduced by HRT (estrogen)
Prevalence of Bone Loss & Fractures in IBD

- IBD patients are at increased risk for bone loss and fracture
  - Approximately **15% have osteoporosis** (T-score < -2.5)\(^1,4\)
  - 5-27% have sustained a fracture\(^2\)
  - **41% increase in fracture risk vs. general population**\(^1\)
- **Osteopenia has been noted in children, young men, premenopausal women with IBD**\(^1,3,5\)
- **Only 13% of IBD patients with fractures receive anti-fracture treatment**\(^2\)

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\(^1\) Bernstein et al., Gastroenterology 2003;124:795-841
\(^2\) vanStaa, et. al., Gastroenterology 2003;125:1591-1597.
\(^3\) Stoffel EM and Wolf JL., Publication of CCFA ,June 2002; 1(4).
\(^5\) Gokhale, et.al.,Gastroenterology 1998;114:902-911.
Risk Factors for Bone Loss in
IBD

- Nutrient malabsorption\(^2,3\)
- Vitamin D deficiency\(^1,2\)
- Inflammatory cytokines: IL-6, IL-1, TNF\(^1,2,3\)
- Hypogonadism\(^2,3,4\)
- Lactose intolerance\(^3\)
- Corticosteroids\(^1,2\)
- Hyperalimentation\(^1\)
- Reduced peak bone mass\(^2\)
- IBD disease state\(^5\)

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\(^3\) Stoffel EM and Wolf JL., Publication of CCFA ,June 2002; 1(4).
Corticosteroid-Induced Bone Loss

- Bone loss occurs early (weeks to months after initiation of therapy)
- Cumulative dose, dosage, and duration of corticosteroids may play a role
- Calcium and small doses of vitamin D may confer limited prophylactic benefit

AGA Recommendations for Managing Osteoporosis

IBD patient:
Any of:
- Prolonged steroid use (>3mo consec or recurrent courses)
- Low trauma, fragility fracture
- Postmenopausal or male age >50
- Hypogonadism

**DEXA**

- T score >-1
- T score -2.5 to -1
- T score <-2.5

**Basic Prevention:**
- Ca/Vit D
- Exercise
- Smoking cessation
- Avoid alcohol
- Minimize corticosteroids
- Treat hypogonadism

**Prevention and:**
- Repeat DEXA 2 years
- Prolonged CS consider BP and DEXA 1 year

**Prevention and:**
- Screen other causes low BMD
- Bisphosphonate therapy or
- Refer to bone specialist

Bernstein et al. *Gastroenterol* 2003;124:795-841
How to be a healthier woman with IBD

- Communicate well with your family and provider
- Maintain remission in pregnancy
- Follow preventive health guidelines: vaccinations, bone density, nutrition
Resources

- United Ostomy Association
  - www.uoa.org
- CCFA
- American Association of Sex Educators, Counselors and Therapists
  - AASECT@worldnet.att.net
- American Association for Marriage and Family Therapy
  - www.aamft.org
- Sexual Information and Education Council of the United States
  - www.siecus.org
Questions?