Pregnancy and IBD: What is Safe?

Amy E. Barto, M.D.
Director
Center for Inflammatory Bowel Disease
Lahey Clinic Medical Center
Burlington, MA

Slide 2

- The diagnosis and treatment of the disease should not be worse than the disease itself.
- The price of liberty is eternal vigilance.
- If you simply look at the single leaf of the tree, you miss the beauty of the thousand leaves.

Outline of Talk

- IBD and pregnancy:
  - Issues surrounding pregnancy
  - Genetics
  - Fertility
    - In general
    - Special considerations in pouch surgery
  - Men and women
    - Conception
    - Fertility
    - Pregnancy
    - Delivery/Fetal Outcomes...
Outline of Talk

- IBD medications during pregnancy:
  - General points to consider
  - FDA pregnancy classifications
  - 5-ASA products (Asacol, Lialda, etc)
  - Steroids
  - Immunomodulators (methotrexate, Imuran/6MP)
  - Biologics (Remicade, Humira, Cimzia, Tysabri)

IBD in Pregnancy: A Hot Topic

- The vast majority of people with IBD are of child-bearing age
- Both men and women will have questions regarding conception, fertility, and pregnancy
- Future plans for family need to be explored BEFORE the pregnancy test is positive

IBD and Pregnancy: A Hot Topic

- Patients and doctors will have their own (often very strong) opinions
- Only limited scientific data available, most studies on medications done with animals
- The internet is often more harmful than helpful
Role of Genetics
- IBD is a combination of genetics and environment
- Lifetime risk for offspring:
  - Jewish descent:
    - Ulcerative colitis: 4.5%
    - Crohn's: 7.8%
  - Non-Jewish:
    - Ulcerative colitis: 1.6%
    - Crohn's: 5.2%
- Couples:
  - Up to 36-50%
  - No difference between when the parent was diagnosed with IBD (either before or after they had kids)
- Genetics also influence disease location and type of IBD
- There is no standard genetic testing for IBD right now

Can I get pregnant if I have IBD?
- IBD affects women during childbearing years (first peak incidence 15 to 30 years)
- Women may be taking certain medications inadvertently at time of conception (some OK/some not OK)
- Conception should be avoided when IBD is active!

IBD and Conception
- IBD affects women during childbearing years (first peak incidence 15 to 30 years)
- Women may be taking certain medications inadvertently at time of conception (some OK/some not OK)
- Conception should be avoided when IBD is active!
Slide 10

IBD and Fertility: The Good News

- People with IBD have normal fertility rates overall (92.2%)
- Crohn's may be slightly lower than UC in certain situations due to scarring in the pelvis from inflammation and adhesions

Slide 11

IBD and Fertility: Additional Info

- Decreased fertility related to ACTIVE disease:
  - Overall toxicity of Crohn's disease from generalized inflammation in the body
  - Decreased sex drive both physically, emotionally
- Patients with IBD (even in remission) have fewer children:
  - If diagnosis of IBD prior to childbearing
  - Relationship difficulties
  - Fear of pregnancy (self and doctor-induced)
  - Body image problems (especially with a stoma)

Slide 12

Bringing Sexy Back!

ostomysecrets.com
IBD and Fertility in Men

- Sulfasalazine (Azulfidine):
  - Affects sperm count, motility and shape
  - 64% of men affected, usually within 2 months
  - Reversible within 3 to 6 months once medication discontinued
  - Switch to a 5-ASA medication (Asacol, Pentasa, Dipentum, Colazal, Lialda, Apriso)

IBD and Fertility in Men

- Methotrexate: caused temporary low sperm count in animals
- Sperm is normal with Imuran/6MP
- Infliximab may affect sperm quality (small study of only 10 patients)
- Reproductive capacity in men not otherwise affected by IBD

Does pouch surgery for UC influence future pregnancies?
Ileal Pouch Anal Anastomosis (IPAA)

- Usually for UC patients
- The entire colon is removed
- The last portion of small bowel is fashioned into a "J pouch"
- This is attached directly to the anus
- Creates a new reservoir for stool like the old rectum
- Stool exits through the anus the old fashioned way
**Pouch Surgery and Fertility**

- Decreased fertility after pouch surgery:
  - Due to pelvic adhesions affecting the fallopian tubes
  - Exclusive to IBD rather than other diseases
  - Can affect a significant number of patients
  - Women can still undergo successful IVF
  - Men can also have infertility after pouches

**Pouch Surgery and Fertility**

- Other options:
  - Choose a diverting ileostomy (bag) until finished having children, then complete the surgery for the pouch
  - Consider a colectomy with an ileorectal anastomosis (no pouch)
  - These decisions need to be made individually with your surgeon and depend on your individual situation
  - Consider banking sperm/eggs

**Other Issues after a Pouch**

- Painful intercourse (approx 20%)
- During pregnancy:
  - Transient increase in day/night stool frequency, anal leakage—resolves after delivery
- Delivery of the baby:
  - Can be done vaginally after a pouch in select circumstances
Cumulative Incidence of Pregnancy Within 5 Years

<table>
<thead>
<tr>
<th>Time to Pregnancy (months)</th>
<th>Before diagnosis</th>
<th>During disease</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>1</td>
<td>0.4</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Adapted from Gastroenterology, Vol 122, Olsen KØ, Juul S, Berndtsson I, Öresland T, Laurberg S, Ulcerative Colitis: Female Fecundity Before Diagnosis, During Disease, and After Surgery Compared with a Population Sample, pages 15-19, Copyright 2002 with permission from Elsevier.

How will my IBD act during pregnancy?

Influence of Pregnancy on IBD

- Course of IBD during pregnancy parallels severity of disease before pregnancy
- Probability of a flare:
  - Generally not increased
  - Most likely within 1st trimester, postpartum
- Outcomes now improved by modern therapy
First Trimester Considerations

- Nausea, decreased appetite, fatigue
- Iron, B12, folate deficiency
- Ionizing radiation
  - Fetal risks of anomalies, growth restriction, or abortions are not increased with radiation exposure of < 5 rad
  - Fetus neurologic development at greatest risk at 8 to 15 weeks
  - No proven risk < 8 weeks or > 25 weeks

Table 1: Estimated Fetal Exposure From Some Common Radiologic Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Fetal Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray (2 views)</td>
<td>0.02-0.07 mrad</td>
</tr>
<tr>
<td>Abdominal film (single view)</td>
<td>100 mrad</td>
</tr>
<tr>
<td>Intravenous pyelography</td>
<td>51 rad</td>
</tr>
<tr>
<td>Hip film (single view)</td>
<td>200 mrad</td>
</tr>
<tr>
<td>Mammography</td>
<td>7-20 mrad</td>
</tr>
<tr>
<td>Barium enema or small bowel series</td>
<td>2-4 rad</td>
</tr>
<tr>
<td>CAT scan of head or chest</td>
<td>&lt;1 rad</td>
</tr>
<tr>
<td>CAT scan of abdomen and lumbar spine</td>
<td>3.5 rad</td>
</tr>
<tr>
<td>CAT enterography</td>
<td>3.5 rad</td>
</tr>
</tbody>
</table>
**Other Tests During Pregnancy**

- Endoscopic studies:
  - Routine studies not recommended
  - Emergency flex sig/colonoscopy can be performed
  - Minimize sedation, particularly versed (versed = D, fentanyl = C, meperidine = B)
- Safety of MRI not well studied
- Ultrasound safe

---

**Second Trimester Considerations**

- Risk of flares low
- 10-20 pound weight gain
- Safest time to operate
- CT OK after 25 weeks

---

**Third Trimester Considerations**

- Anemia can be severe
- Increased risk of preterm births
- Corticosteroids - monitor size of baby by serial ultrasound
- Stress dose steroids during labor if needed

IBD and Delivery

- UC = normal vaginal delivery
- Patients with Crohn’s more likely to have a Cesarean section (20% vs. 15%), whether or not it is indicated
- Episiotomies contraindicated in a patient with a history of perianal Crohn’s:
  - Trauma can exacerbate fistula formation
  - Some patients can experience new perianal Crohn’s after vaginal delivery with episiotomy
- Cesarean for ACTIVE perianal disease with or without fistulas

IBD and Delivery: Pouches

- Vaginal delivery considered safe for select patients with pouches
- Anal sphincter function can be affected by vaginal delivery, may affect subsequent overall pouch function
- Pouch function generally returns to baseline after delivery, long-term changes (10-20 years) unknown

IBD and Fetal Outcomes

- Overall complication rates generally parallel the general population
- Pregnancy itself is not without risk: 2-3% background risk of congenital malformations in the general population
- In those with IBD who had complications, 62% of mothers had active Crohn’s
Complications likely relate to disease activity rather than drugs.
Fetal mortality high if surgery required during pregnancy (best performed in second trimester).
Active Crohn’s a known risk for:
- Preterm delivery
- Small birth weights
- Consider a high risk OB if you have active disease during pregnancy.

Even mothers with Crohn’s in remission are at risk for SGA babies.
Smoking and small bowel disease are independent risk factors.
Slide 37

“The worst scenario is a sick mother”
-Dan Present, MD

“The greatest risk to pregnancy is active disease—not active medicine”
-David Sachar, MD

Slide 38

Challenges
- Fear on the part of patients: “I don’t want to take ANYTHING to harm my baby”
- Fear on the part of physicians: wanting to avoid additional risks for mother and baby
- Conflicting opinions within and between obstetrics, gastroenterologists
- Conflicting opinions on the internet
- Limited available clinical data

Slide 39

IBD Medications and Pregnancy
- IBD should be well-controlled before conception
- Whatever was used to achieve remission should be continued during pregnancy (within guidelines)
- The main priority is to maintain remission throughout pregnancy
- The risks associated with medications are far less than the risks of active IBD during pregnancy:
  - Fetal mortality with emergent surgery during pregnancy can exceed 50%
FDA 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 situations when safer drugs are ineffective
- X: Contraindicated in pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Category</th>
<th>Pregnancy</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lialda, Apriso, Pentasa, Colazal</td>
<td>B</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Asacol, Dipentum</td>
<td>C</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Metronidazole (Flagyl)</td>
<td>B</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Remicade, Humira, Cimzia</td>
<td>B</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Cipro</td>
<td>C</td>
<td>Debated</td>
<td>Not safe</td>
</tr>
<tr>
<td>Steroids</td>
<td>B/C</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Azathioprine/6MP</td>
<td>D</td>
<td>Safe</td>
<td>Likely Safe</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>C</td>
<td>w/caution</td>
<td>Not safe</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
<td>Not safe</td>
<td>Not safe</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>X</td>
<td>Not safe</td>
<td>Not safe</td>
</tr>
</tbody>
</table>

2. Can affect cartilage development

3. Based on new evidence
**Safety of IBD Medications During Pregnancy**

**Category B**
- Loperamide (Imodium)
- Mesalamine (Pentasa, Lialda, Apriso)
- Balsalazide (Colazal)
- Corticosteroids (prednisone)
- Sulfasalazine
- Metronidazole*

*Second and third trimester

---

**Summary: Safety of IBD Medications During Pregnancy**

**Category C**
- Budesonide (Entocort)
- Ciprofloxacin
- Cyclosporine
- Diphenoxylate (Lomotil)
- Olsalazine (Dipentum)
- Tacrolimus
- Natalizumab (Tysabri)

---

**Category D**
- Azathioprine†
- 6-Mercaptopurine†

Summary: Safety of IBD Medications During Pregnancy

Category X
- Methotrexate
- Thalidomide

Sulfasalazine (category B)
- Not associated with prematurity, low birth weight, or spontaneous abortion
- Interferes with folate absorption:
  - Important in pregnancy
  - Supplement with folate 1 mg BID
- No adverse effects from nursing
- Consensus: safe

5-ASA Drugs (category B, C)
- Category B, except Olsalazine (Dipentum) and Asacol which are Category C
- Widely used safely during pregnancy
Slide 49

**Antibiotics**

- Use in short courses (2 to 3 weeks)
- Metronidazole = category B
  - Avoid in first trimester
  - Probably safe in 2nd, 3rd trimester
- Ciprofloxacin = category C
  - Use with caution, can affect cartilage development
- Rifaximin
  - Not well studied

Slide 50

**Corticosteroids (category B)**

- Small risk to fetus with temporary high doses
- Associated with low birth weight and stillbirths (related to disease activity)
- Can cause glucose intolerance, hypertension in mom
- Consensus: safe
- Most choose to continue with steroids during pregnancy rather than introduce a stronger drug for the first time

Slide 51

**Azathioprine/6MP (category D)**

- Only small studies available:
  - Retrospective study:
    - 16 pregnancies in 14 patients treated with AZA
    - No congenital abnormalities
    - No maternal or neonatal problems in clipping
    - Case-control study:
      - 155 subjects exposed to 6-MP
      - No increase in prematurity, spontaneous abortions, congenital abnormalities, or childhood infections/neoplasms
- Consensus: safe, use with caution if introducing during pregnancy
- New evidence shows may be safe in breastfeeding

**Slide 52**

**Cyclosporine (category C)**
- Tricky because often introduced as a brand new medication during a flare
- Use with caution in late pregnancy
- Multiple potential side effects, most notably hypertension and seizures
- Best when used as salvage therapy to avoid/delay a potentially high risk surgery
- Consensus: safe with close monitoring

---

**Slide 53**

**Biologics**
- Class B: Remicade, Humira, Cimzia
- Class C: Tysabri
- Post-marketing registries will continue to expand our data on the safety of these medications
- All of these medications cross the placenta
  - Remicade and Humira by active transport
  - Cimzia by passive diffusion, levels minimal to none in fetus

---

**Slide 54**

**Biologics**
- Options for delivery:
  - Hold 3rd trimester dosing
  - Continue dosing through delivery to avoid a flare
  - Baby needs to be safe for the live rotavirus vaccine at 2 months
  - Breast-feeding is considered safe
PIANO Registry

- Pregnancy registry by Uma Mahadevan, MD
- Over 1,000 patients registered since 2007
- Follows women with IBD throughout pregnancy, delivery, children to age 1
- Patients who received during pregnancy:
  - No immunomodulators or biologics
  - Yes immunomodulators, biologics
- NO increased risk of complications or congenital abnormalities with these medications

Additional Drugs: Not Safe

- Methotrexate (category X):
  - Folic acid antagonist
  - Highly mutagenic and teratogenic
  - Neural tube and other defects
  - Consensus: not safe, mandate a form of birth control
  - Discontinue for at least 3 months (some recommend 12 months) prior to pregnancy
- Thalidomide (category X):
  - Multiple birth defects
  - Consensus: not safe

Summary: Medications

- Yes: 5-ASA, steroids, 6-MP/AZA
- Yes: Infliximab, adalimumab, certolizumab
- Consider stopping done 10 weeks (infliximab) or 4-6 weeks (adalimumab) prior to due date
- Certolizumab can be maintained throughout pregnancy
- No: Methotrexate, thalidomide, diphenoxylate
### Slide 58

<table>
<thead>
<tr>
<th>Medication</th>
<th>Category</th>
<th>Pregnancy</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lialda, Asacol, Pentasa, Colazal</td>
<td>B</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Asacol, Dipentum</td>
<td>C</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Mesalamine (eg., PediaCare)</td>
<td>B</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Pentasa, Humex, Geara</td>
<td>B</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Cipro</td>
<td>C</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Entacan</td>
<td>B</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Azathioprine/6MP</td>
<td>D</td>
<td>Safe</td>
<td>Likely Safe</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>C</td>
<td>w/caution</td>
<td>Not safe</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
<td>Not safe</td>
<td>Not safe</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>X</td>
<td>Not safe</td>
<td>Not safe</td>
</tr>
</tbody>
</table>

1. 2nd and 3rd trimester
2. Can affect cartilage development
3. Based on case evidence

### Slide 59

**The Bottom Line:**

You should consider: Where does the true gamble come into play when considering stopping your IBD medications during pregnancy?

If it took medication to keep you in remission, stay on medication during pregnancy.

### Slide 60

**Summary**

- Pregnancy itself is not without risk.
- Active IBD is a strong risk factor for adverse pregnancy outcomes.
- The course of IBD during pregnancy is generally the same as pre-pregnancy.
- Despite remission, IBD may still be a risk factor for pre-term delivery, low birth weight infants.
Summary

- IBD should be kept in remission during pregnancy.
- The use of standard IBD drugs (except methotrexate and thalidomide) is generally safe in pregnancy.
- Maintenance treatment for IBD is not only safe but crucial in pregnancy.
- Talk to your doctor!