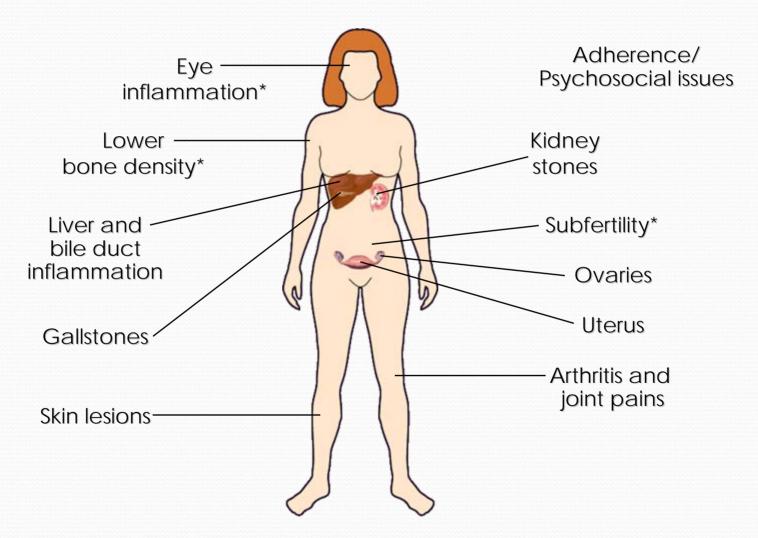
Women's Health Issues in IBD

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November 19, 2010

IBD: Systemic Complications



Influence of Gender on Illness-Related Concerns in IBD

- Study of 343 men and women
 - Women report higher levels of symptom severity (*P*=.04)
 - Higher levels of of concerns with IBD (*P*<.001)

Patients' Concerns in IBD

- Greater in Women Than in Men
 - Feelings about body
 - Attractiveness
 - Feeling alone
 - Having children
 - Intimacy (CD)
 - Sexual performance (CD)

Gender-Related Considerations in IBD

	Women	Men
Reproductive issues	↓ fertility after IPAA or proctocolectomy	√fertility with sulfasalazine
	↑ risk of relapse if disease active at time of conception	↓Sperm count with methotrexate
Disease-related concerns	↑ concern re: body stigma, loss of bowel control	
Sexuality		↓ libido and sexual satisfaction after proctocolectomy

Special Considerations for Women With IBD

- Cervical Dysplasia
- Menstruation/contraception
- Body image/sexuality
- Conception/pregnancy/breast-feeding
- Menopause/hormone replacement therapy
- Risk of osteoporosis
- Adherence
 - Physician-patient partnership
- Overlapping IBS

Cervical Dysplasia

- Human papilloma virus (HPV) is the most important risk factor for cervical neoplasia
- Age, nutritional status, immune function, and smoking also play a role
- The HPV vaccine (Gardasil, Merck) is indicated for the prevention of cervical dysplasia caused by HPV high-risk types 16 and 18 (6 and 11 - genital warts)
 - recommended for ages 9 to 26 prior to the initiation of sexual activity and those already engaged in intercourse

Incidence of Abnormal Pap Smears in IBD

- Women with IBD taking immunosuppressive therapy have higher prevalence of abnormal Pap smears than age-matched controls
 - young female smokers are particularly susceptible
- Adjusted for smoking, OCP use and parity
- Use of azathioprine increased risk 3 fold

Cervical dysplasia and IBD

- Vaccinate regardless of sexual activity
- Screen for cervical intraepithelial neoplasia (CIN) and cancer in both vaccinated and unvaccinated women
 - annually
 - young female smokers on immunosuppressive therapy with IBD should be recognized as a vulnerable population

Menstrual Cycle and Bowel-Pattern Fluctuations

- Bowel-pattern fluctuation is common during the menstrual cycle
- IBD symptoms may increase during the menstrual cycle
- Suppression of menses via hormonal contraceptive methods may be considered in presence of debilitating symptoms

Potential IBD-Related Menstrual Symptoms

Most frequently reported symptoms

Pelvic pain 52%

• Lower back pain 36%

• Diarrhea 26%

Irritability 23%

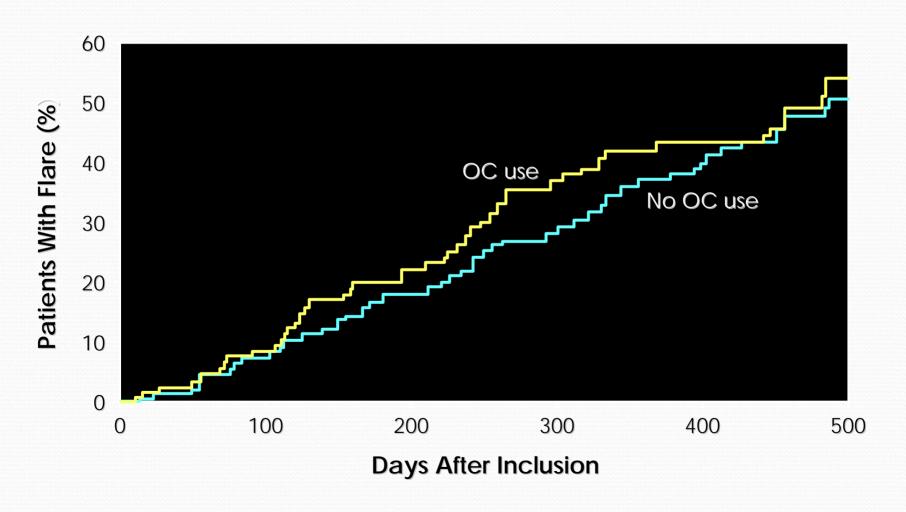
• Headache 20%

 Incidence of any menstrual symptoms significantly higher for IBD patients than for healthy controls (p≤.01)

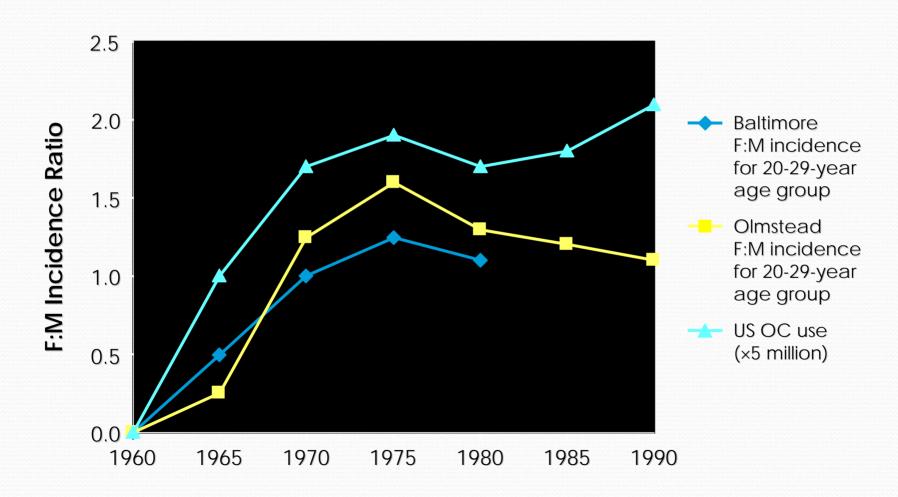
OCPs and IBD Risk

- Controversial data
- Increased incidence of CD with use of OCs?
- OCs related to flare of CD activity?
- Newer OCs with lower estrogen content associated with decreasing incidence of CD in women?

CD Flare and OCPs



OCPs and IBD Risk



Adapted from Alic M. Gut. 2000;46:140.

IBD and Contraception: Conclusions

- OCPs should have lower estrogen content (eg, ≤35 μg)
- Avoid for women with known hypercoagulability
- Avoid for women with IBD-associated liver disease
- Avoid for women with IBD who smoke

IBD and Sexuality: Physical Impact

- Impact of disease
 - Perianal complications
 - Draining cutaneous fistulae
 - Skin lesions
 - Arthritic deformities
 - Pain
 - Fatigue

- Impact of treatment
 - Surgical scars
 - Stoma
 - Medication side effects

IBD and Sexuality: Psychological Impact

- Affected aspects
 - Behavior patterns
 - Communication
 - Sexual drive
 - Sensations connected with sexual activity

- Negative effects
 - Feeling dirty, unsexy, unattractive
 - Reduced self-esteem
 - Loss of former identity
 - Anxiety over disclosure

Sexual Function and IBD

- No difference in rates of sexual activity
- Depression a bigger determinant of lower sexual activity
- Women with IBD more likely to have vaginal dryness, dyspareunia, vaginal infections than healthy controls
- Only 25% of patients wanted to discuss sexuality with their physician

Sexual Function Following IPAA

- Usually improved because of improved general wellbeing
- Some problems may continue
 - Dyspareunia
 - Vaginal drying
- Sexual function improved 16%-25%
- Frequency of intercourse increased 35%

Gynecologic Function Before and After IPAA

	Before	After
Dyspareunia*	5%	15%
Fecal incontinence during intercourse	3%	7%
Menstrual problems	23%	31%

Counihan TC, et al. *Dis Colon Rectum*. 1994;37:1126-1129. Tiainen J, et al. *Scand J Gastroenterol*. 1999;34:185-188. Sjogren B, Peppen B. *Acta Obstet Gynecol Scand*. 1995;74:51-55. Damgaard B, et al. *Dis Colon Rectum*. 1995;38:286-289. Bambrick M, et al. *Dis Colon Rectum*. 1996;39:610-614.

^{*}Rates range from 0% to 26%.

Women With Ileostomies: Sexual Function

% Patients

No change	47%

- Adversely affected 47%
 - Mild (22%)
 - Severe (14%)
 - Moderate (11%)
- Improved7%

Women With Ileostomies: Sexual Concerns

Sexual attractiveness decreased 52%

Appliance 72%

• Stoma 16%

• Odor 4%

- More women (60%) than men (52%) felt less desirable
- Sexual intercourse is more difficult

Psychologically 46%

Physically 32%

Conception and Fertility in Women with IBD

- Highest age adjusted incidence rates of IBD (15 30) overlap peak reproductive years
- Improved medical and surgical treatment of IBD has allowed patients with more significant illness to consider having children
- Optimal treatment algorithms for IBD patients during pregnancy have not been defined, including issues regarding high risk pregnancy
- Optimal management of reproductive health in IBD patients is a challenge to gastroenterologists, obstetricians, IBD surgeons

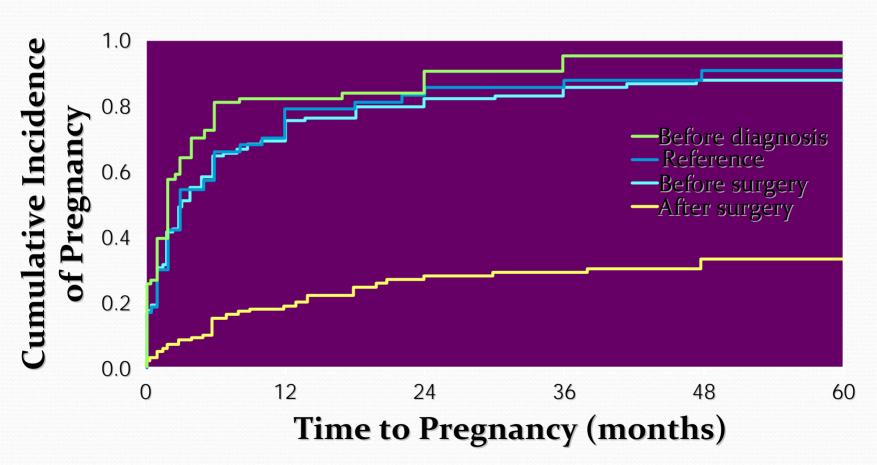
Goals: Pregnancy and IBD

- Fertility becoming pregnant
- Having an uneventful term pregnancy:
 - Avoiding preterm delivery
 - Avoiding severe flare during pregnancy
- Use of safe medications to maintain remission in mother during pregnancy
- Use of safe medications in post-partum period while breastfeeding to help mother maintain remission and keep infant safe

IBD patients have fewer children

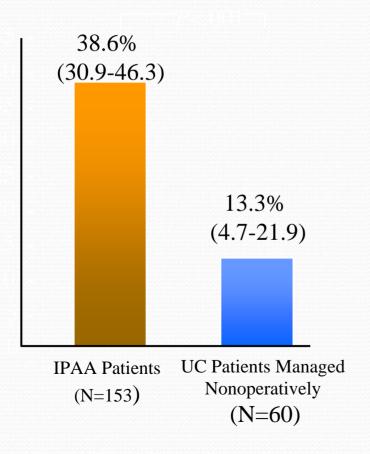
- Fear of pregnancy
- Fear of disease transmission to offspring
- Relationship difficulties
 - Fear of intimacy
 - Dyspareunia and decreased libido
- Body image issues
- Incorrect medical advice

IPAA: Cumulative incidence of pregnancy within 5 years

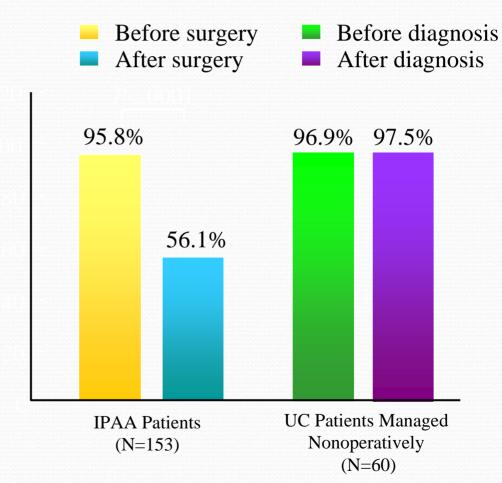


Female infertility after IPAA for UC

Infertility Rate (95% CI)



Success Rate in Becoming Pregnant (%)



Infertility after IPAA: why?

- Post-operative adhesions
 - Obstructing fallopian tubes (~50%)
 - Altering normal tubo-ovarian relationship needed for normal ovum capture and transport
- Damage to the reproductive organs and nerve plexuses
- ? Age at IPAA
- Decreased fertility/fecundity in other populations
 - FAP patients after IPAA (54%)
 - Patients who undergo proctocolectomy with ileostomy (~63%)

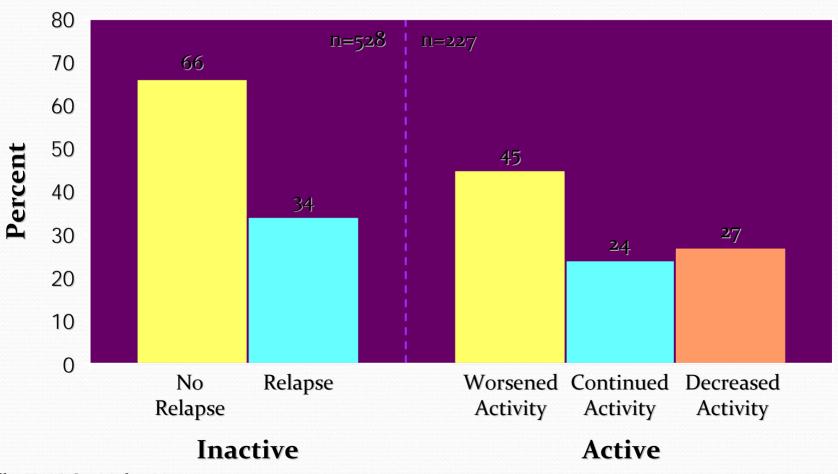
Fertility and Crohn's

- Fertility rates are similar between CD patients and general population
- Decreased fertility as a result of disease activity, normalized when remission achieved
- In 5 studies, inability of patients to conceive because of CD ranged from 12 to 67 %
- Surgery for CD can impact fertility

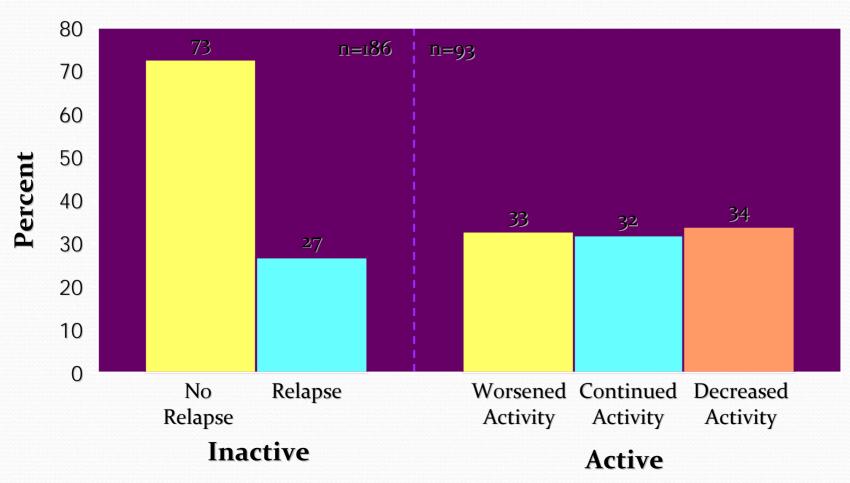
Infertility rates and Crohn's: conflicting findings

Author (yr)	N	Crohn's	Control
Fielding 1970		22%	
	77	32%	
Khosla 1984	54 (married)	12%	10% (general population)
Mayberry 1986	224 (married)	42%**	28%
Baird 1990	177	5%	8%
Hudson 1997	123	14%*	14%

Effect of pregnancy on UC: disease activity at conception



Effect of pregnancy on CD: disease activity at conception



General considerations

- Preterm delivery is the second leading cause of neonatal mortality in the United States
- Known risk factors for preterm birth
 - black race
 - single marital status
 - low socioeconomic status
 - cigarette smoking
 - inadequate prenatal care
 - less education
 - reduced social support



Effect of IBD on birth outcomes: State of Washington, 1987-96

	UC	CD	Controls	OR, UC	OR, CD
	n=107	n=155	n=1308	(95% CI)	(95% CI)
LBW (<2500 g)	7.6%	16.8%	5.3%	1.1 (0.4-3.3)	3.6 (2.2-5.9)
Preterm	10.4%	15.2%	7.2%	1.0 (0.4-2.5)	2.3 (1.4-3.8)
SGA	10.5%	15.2%	5.3%	1.7 (o.8-3.8)	2.3 (1.3-3.9)
Congenital Abr	nl 7.9%	3.4%	1.7%	3.8 (1.5-9.8)	2.0 (o.8-5.5)
C-section	28.7%	28.4%	20.2%	1.3 (0.8-2.2)	1.6 (1.1-2.3)

Adjusted model is presented because there were no covariates that altered the unadjusted odds ratio by at least 10%

Effect of IBD on birth outcomes: Sweden, 1991-92

	IBD	No IBD	Adjusted OR
	n=756	n>239,000	(95% CI)
Late fetal death	0.5%	0.3%	1.3 (0.6-2.6)
Infant death	0.5%	0.5%	
LBW (<2500 g)	1.2%	0.6%	2.2 (1.1-4.2)
Very Preterm (<32 wk)	1.9%	1.0%	1.8 (1.1-3.1)
Preterm (<37 wk)	6.3%	4.3%	1.5 (1.1-2.0)
SGA	4.0%	2.9%	1.4 (0.97-2.0)
C-section	15%	10%	1.5 (1.2-1.8)

Effect of IBD on birth outcomes: Northern CA Kaiser Permanente, 1995-2002

	Patients without IBD	IBD patients	p value
N	493	461	
Mean age at conception, y (SD)	30 (±6.0)	30 (±5.8)	_
Mean number of prenatal visits (SD)	8 (4.5)	6.9 (5.5)	<.01
Current smoker	14.4%	9.2%	.02
Current alcohol use	11.5%	3.9%	<.01
Mother's ethnicity			
Caucasian	52%	68%	
Asian	14%	5%	
Black	14%	13%	
Hispanic	13%	11%	
Other	7%	3%	
Type of IBD	_		
CD		154	
UC		300	
Indeterminate colitis		7	
Mean IBD duration, y (SD)	_	5.7 (±5.6)	
History of surgery for IBD	_	87 (15%)	
Any immunosuppressant	2 (0.6%)	19 (4%)	<.01
use			
CD		10 (6.6%)	
UC		9 (3%)	
Any salicylate use	1 (0.3%)	234 (51%)	<.01
Any steroid use	0	96 (21%)	<.01

Effect of IBD on birth outcomes: Northern CA Kaiser Permanente, 1995-2002

	Non-IBD	IBD	P-value
	(n=493)	(n=461)	
Adverse conception outcomes (SAb, TAb)	62 (17%)	83 (23%)	P = 0.03
Adverse pregnancy outcomes (SGA, Preterm, Stillbirth)	58 (19%)	70 (25%)	P = 0.05
Complicated labor/pregnancy	47 (16%)	68 (25%)	P < 0.01
Adverse neonatal outcome (NICU, death, seizure)	22 (7%)	28 (10%)	P = 0.18
Cesarean section	38 (9.5%)	61 (13.8%)	P = 0.05
Congenital anomalies	30 (6%)	34 (7%)	P = 0.71

Kaiser Permanente: predictors for adverse outcomes

Conception outcome

Diagnosis of IBD

(1.65, 1.09 – 2.48)

Non-Caucasian ethnicity

(2.42, 1.28 - 4.55)

• IBD surgery (vs controls)

(2.26, 1.12 - 4.55)

Pregnancy outcome

• Diagnosis of IBD

(1.54, 1.00 - 2.38)

Non-Caucasian ethnicity

(2.90, 1.45 - 5.78)

Pregnancy complications

Diagnosis of IBD and CD

(1.78, 1.13 - 2.81); (2.33, 1.24 - 4.37)

• IBD surgery (vs controls)

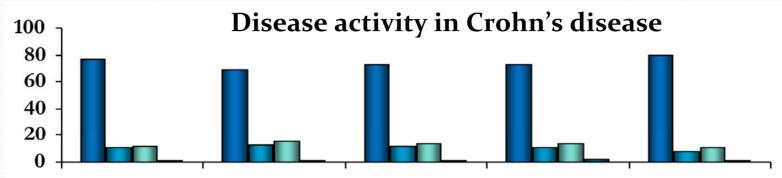
(2.99, 1.39 - 6.43)

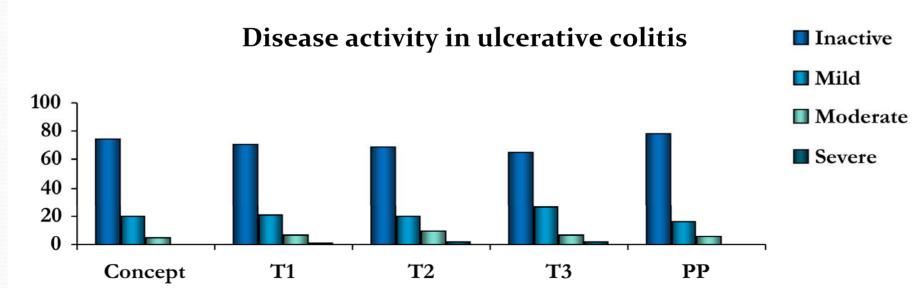
Newborn outcome

Diagnosis of CD

(3.20, 1.33 - 7.73)

Effect of pregnancy on IBD - 1





Mahadevan U et al. Gastroenterol. 2007:1106-1112

Effect of pregnancy on IBD - 2

- Earlier studies suggest that disease activity is a predictor of adverse outcome in pregnancy
 - Increased risk of preterm birth, fetal loss, LBW, spontaneous abortion
- More recent studies show that disease activity does not increase this risk more than expected with IBD alone
 - Few patients on immunosuppressants (4-10%)
 - Few patients with moderate to severe disease activity (5-14%)

Pregnancy outcomes: summary

- Women with IBD are more likely to have adverse outcome related to gestation than women without IBD
 - Preterm birth
 - ↑ risk in both UC and CD
 - Significant 1 in risk of low birth weight
 - ↑ risk of maternal/delivery complications
- No overall observed difference in newborn outcomes; may be present in CD
- No major impact on risk of congenital abnormalities
- Limited data on the effect of disease activity and IBD medications

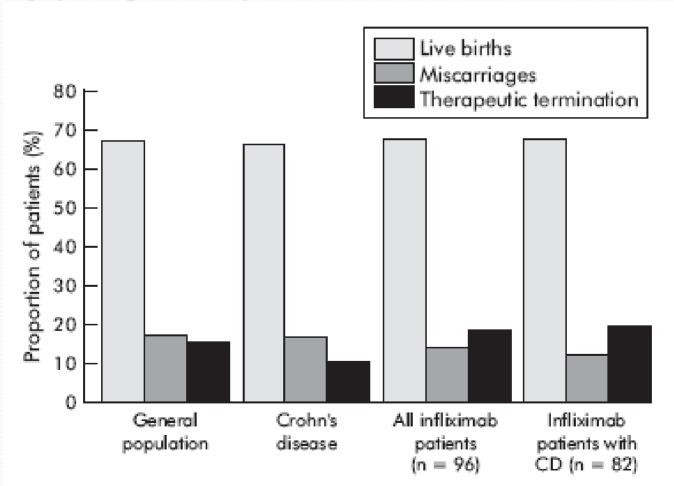
Perianal Crohn's Disease and pregnancy

- Women with perianal CD and no prior history of perianal symptoms or inactive symptoms are at very low risk of relapse
- Active perianal disease at time of delivery: Csection recommended
- Episiotomy and perianal trauma (i.e. laceration) does not seem to predispose to perianal disease in patients with or without a history of perianal CD

Summary: safety of IBD medications during Pregnancy

Category B	Category C	Category D	Category X
Loperamide	Ciprofloxacin	Azathioprine	Methotrexate
Mesalamine	Cyclosporine	6-Mercaptopurine	Thalidomide
Balsalazide	Diphenoxylate		
Sulfasalazine	Olsalazine		
Anti-TNF agents	Tacrolimus		
Metronidazole	Natalizumab		
	Corticosteroids		

Outcomes of women exposed to infliximab during pregnancy



Mahadevan U *Gut* 2006:1198-1206l Katz JA, et al. *Am J Gastroenterol*. 2004;99:2385-2392. Ventura et al. National Center for Health Statistics Vital Health Stat 2000;21:1-59

Infant outcomes: PIANO Registry

- PIANO: Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes
- One-year data of a 6-year study
- 600 women enrolled; 1000 expected
- Pregnancy and fetal outcomes among women treated with 6MP/Azathioprine, and control
- So far:
 - no consistent association with drug exposure and rate of pregnancy complications or birth defects up to 12 months
 - Out of 600 live births, five birth defects were noted at birth, and 17 were noted after one year

In practice.....

- 6-MP/AZA
 - No clear association with congenital malformations
 - Breastfeeding has traditionally been discouraged, but recent data showing zero to minimal levels in breast milk and no detectable levels in the infant
- Biologics
 - Continue drug to keep pregnant patient in remission
 - Last dose of infliximab early in 3rd trimester and the next dose after birth
 - ? monitoring infliximab levels in infant until not detectable
 - Adalimumab and certolizumab can be used in pregnancy
 - Avoid live rotavirus vaccine in the infant
- Combo therapy
 - If in remission, may stop the immunomodulator to minimize risk and comfortably breastfeed

Menopause

- Natural menopause results from gradual decline in number of estradiol-producing ovarian follicles
- Surgical menopause may occur at any age as a result of oophorectomy
- Estradiol decreases; estrone becomes primary circulating hormone
- Testosterone declines at varying rate
- No data on effect of menopause on IBD

HRT Protective Against Disease Activity After Menopause

- Cohort of post-menopausal women
- Disease activity pre and post menopause
- Those taking HRT less likely to have a disease flare in
 years post menopause
- Dose response for length of use
- Form of menopause did not matter

Potential Benefits vs Risks of HRT

Potential Benefits

- Decrease in vasomotor symptoms
- Slower changes in body morphology
- Fewer osteoporotic fractures
- Improvement in lipid balance
- Reduce IBD flare

- Increase in invasive breast cancer
- Side effects: bloating, irritability, weight gain, depression, vaginal bleeding
- Increased risk of thromboembolic events (blood clots, stroke)
- Increase in CVD

HRT Guidelines for IBD Patients

- As with all therapeutic choices, therapy for menopausal symptoms should be individualized
- For women with severe osteopenia or osteoporosis, HRT benefits may outweigh risks if alternatives are not feasible
- For women at increased risk for breast cancer, HRT risks may outweigh benefits
- CVD risk vs benefit is controversial, but risk may outweigh benefit

General Risk Factors for Osteoporosis

- Advancing age
- Female gender
- Family history
- Alcohol use
- White/Asian race

- Smoking
- Physical inactivity
- Low calcium intake
- Small and thin body habitus

Risk of Osteoporosis in IBD

- Low bone mass in 31% to 59% of IBD patients
- IBD-related risk factors
 - Onset of IBD before reaching age of peak bone mass
 - Inflammatory cytokines (IL-6, TNF-alpha)
 - Calcium malabsorption
 - Vitamin D deficiency (CD patients)
 - Drugs (corticosteroids, methotrexate, cyclosporine)

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

Reducing the Risk of Osteoporosis

History and physical lab (25-hydroxy vitamin D, albumin, calcium, PTH, TSH)

Bone density (DEXA)

Minimize corticosteroids

Low BMD: T Score <-1 SD	Osteoporosis: T Score <-2.5 SD
Hormone (if appropriate)	Hormone (if appropriate)
Raloxifene (if appropriate)	Raloxifene (if appropriate)
Calcium	Calcium
Vitamin D	Vitamin D
General guidelines	Bisphosphonates
Repeat DEXA	General guidelines
	Repeat DEXA
	Hormone (if appropriate) Raloxifene (if appropriate) Calcium Vitamin D General guidelines

Infliximab in Patients With CD and Osteoporosis

- Prospective, 4-week trial with patients taking corticosteroids
- Significant decrease in CDAI with infliximab (*P*=.0001)
- Increase in surrogate markers for bone turnover
- Conclusion: increased bone synthesis with no increase in bone resorption

Prevention and Treatment of Osteoporosis in IBD

- Prevention
 - Baseline measurements of bone density (DEXA) and 25-OH
 Vitamin D
 - Lifestyle and nutritional measures (eg, weight-bearing exercise, smoking cessation, calcium supplementation)
 - All CD Ca+ 500 mg bid-tid and vitamin D 800-1000 IU qday to titrate to 25(OH)D > 30 ng/ml
- Treatment
 - Bisphosphonates (consider IV)
 - Ca/Vitamin D
 - Avoid chronic steroids