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Women's Health Issues in IBD

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Objectives

- Gender differences in clinical course
- Influence of menstruation and IBS
- Body image and sexual dysfunction
- Contraception
- Cervical dysplasia
- Fertility
- Pregnancy and breastfeeding
- Hormone replacement therapy and osteoporosis

Gender differences in clinical course

- Increased prevalence of extraintestinal manifestations
 - Oral aphthae
 - Erythema nodosum and pyoderma gangrenosum
 - Joint symptoms
 - Ocular manifestations

Gender differences in clinical course

- Increased disease severity
 - Mortality
 - Smoking effects on colitis and need for immunosuppressants
 - Increased risk for first intestinal resection
 - Increased risk for osteoporosis

Menstrual cycle and IBD

- Hormonal fluctuations can influence GI symptoms in all women
- Diarrhea is more common in Crohn's disease and IBS than controls before and during menses
- Careful menstrual history with attention to any cyclic alteration in bowel function may be important in determining true disease exacerbation

IBS and IBD

- 33-39% of patients with UC and 42-60% of patients with CD in remission meet Rome II criteria for IBS
- Coexisting IBS vs. occult inflammation
- Higher fecal calprotectin levels were seen in CD and UC patients with IBS-type symptoms than those without

Body image

- More women report negative body image than men (75% vs. 51%, $p < 0.001$)
- 96% of operated females report a negative impact of IBD on body image vs. 61% of non-operated females ($p < 0.0001$)
- Impact of disease: perianal disease, enterocutaneous fistulae, skin manifestations, arthritic deformities
- Impact of treatment: surgical scars, stoma, medication side effects

Sexual dysfunction

- More women than men report decreased sexual activity because of IBD (66 vs. 41%, $p < 0.0001$)
- Women are 3.5x more likely to report decreased libido
- Universal symptoms: abdominal pain, fatigue, fear of incontinence
- Female-specific mechanical issues: dyspareunia, lubrication issues, and vaginal discharge

Sexual dysfunction

- Significantly affects quality of life
- Only 19% of patients reported discussing sexual health with their gastroenterologist
- Depression is a bigger determinant of lower sexual activity
- Need to increase provider and patient awareness of potential for sexual dysfunction and willingness to address it

Contraception

- Barrier methods
- Intrauterine devices (IUD)
- Oral contraceptives (OCP)
- Transdermal/vaginal hormonal contraception

Contraception: OCP and risk of IBD

- Association between OCP use and IBD
- Confirmed in a meta-analysis
 - Pooled RR for CD was 1.46 ($p < 0.001$, adjusted for smoking)
 - Pooled RR for UC was 1.28 ($p = 0.01$, adjusted for smoking)
- RR loses significance after discontinuation of OCP

Contraception: OCP and disease-specific issues

- No significant increased risk of disease relapse
- Absorption occurs in the small bowel and may be impaired with inflammation or resection
- Plasma concentrations of steroid hormones in UC patients s/p colectomy are similar to non-IBD
- Other routes of administration can be considered

Contraception: OCP and thrombosis

- 3.5-fold increased risk of thrombosis with IBD
- The risk of thrombosis increases with age and smoking
- The use of OCP may compound the risk of thrombosis
- Current OCPs are low estrogen formulations which has been shown to decrease stroke risk

Cervical dysplasia

- Conflicting data exists about the risk of cervical dysplasia in IBD
- HIV, transplant, and lupus literature suggests immune suppression is associated with abnormal Pap smears
- ACOG recommends yearly screening for women with HIV, and that recommendation should likely be extended to all patients on immune suppression
- HPV vaccination is indicated in females 9-26

Fertility: Voluntary Childlessness

- IBD patients have a higher rate of voluntary childlessness
- Women with IBD have fewer children
- Contraceptive choices and adoption rates are similar to the general population

Fertility: Ulcerative colitis

- Women with UC have similar rates of fecundability as the general population
- Rates of fertility markedly decrease after IPAA
 - 12% infertility before IPAA and 26% after
 - Lifetime chance of having at least 1 birth is 80%
- Reduction in fertility is likely a result of pelvic dissection in creation of the pouch

Fertility: Crohn's disease

- Overall, rates of fertility in CD are similar to the general population
- Some studies showing increased infertility in CD did not account for disease activity and surgical history
- Others showed decreased fertility in the setting of disease activity, with normalization after remission
- Higher rate of infertility with surgery (12% vs. 5%)

Pregnancy: Effect on disease activity

- Flare rates in UC are similar in pregnancy
 - UC: 34% during pregnancy and 32% when not pregnant
 - CD: 26-34% in the pregnant population, similar to non-pregnant population
- Breastfeeding has not been proven to contribute to disease activity independent of medication cessation

Pregnancy: Outcomes in IBD

- Population-representative cohort of 461 women with IBD
- Increased rates of spontaneous abortion (OR = 1.65, 95% CI 1.09-2.48)
- Increased rates of stillbirth, preterm birth, or small for gestational age (SGA) infant (OR = 1.54, 95% CI 1.00-2.38)
- Increased rates of complication of labor (OR = 1.78, 95% CI 1.13-2.81)
- No difference in congenital malformations

Pregnancy: Outcomes in IBD

- Meta-analysis of 12 studies totaling 3907 patients with IBD
- Increased rates of preterm birth (OR 1.87, 95% CI 1.52-2.31)
- Increased rates of low birth weight (OR 2.1, 95% CI 1.38-3.19)
- Increased risk of congenital anomalies (OR 2.37, 95% CI 1.47-3.82) in UC, but primarily based on 1 study

Pregnancy: Medications

FDA Category	Definition
A	Controlled studies in animals and women show no risk in the first trimester, and possible fetal harm is remote
B	Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester.
C	No controlled studies in humans have been performed, and animal studies have shown adverse events, or studies in humans and animals not available; give if potential benefit outweighs the risk.
D	Positive evidence of fetal risk is available, but the benefits may outweigh the risk if life-threatening or serious disease.
X	Studies in animals or humans show fetal abnormalities; drug contraindicated

Pregnancy: Aminosalicylates

Drug	FDA category	Pregnancy	Breastfeeding
Mesalamine*	B	Low risk	Potential diarrhea
Balsalazide	B	Low risk	Potential diarrhea
Sulfasalazine	B	Low risk, give folate 2mg daily	Potential diarrhea
Olsalazine	C	Low risk	Potential diarrhea

*Asacol recently changed to category C because of presence of dibutyl phthalate in the coating

Pregnancy: Antibiotics

Drug	FDA Category	Pregnancy	Breastfeeding
Metronidazole	B	Avoid in 1 st trimester (small risk of cleft lip)	Potential toxicity
Quinolones (e.g. ciprofloxacin)	C	Avoid, potential toxicity to cartilage	Probably compatible
Rifaximin	C	No human data, some risk in animal data	Unknown

Pregnancy: Glucocorticoids

Drug	FDA Category	Pregnancy	Breastfeeding
Corticosteroids	C	Increased risk of oral clefts in 1 st trim., theoretical risk for gestational diabetes and adrenal suppression in newborn in 2 nd /3rd	Compatible
Budesonide	C	Limited human data	Unknown

Pregnancy: Immunomodulators

Drug	FDA Category	Pregnancy	Breastfeeding
Methotrexate	X	Contraindicated; teratogenic	Contraindicated
Azathioprine/6-mercaptopurine	D	Low risk in IBD and transplant literature	Limited transfer, likely compatible
Cyclosporine	C	Low risk	Likely toxicity
Tacrolimus	C	Low risk	Likely toxicity
Thalidomide	X	Contraindicated; teratogenic	Likely toxicity

Pregnancy: Anti-TNF

Drug	FDA Category	Pregnancy	Breastfeeding
Infliximab (IFX)	B	Low risk, but crosses placenta and detectable in infants after birth	Likely compatible
Adalimumab (ADA)	B	Low risk, likely crosses placenta	Likely compatible
Certolizumab pegol (CZP)	B	Low risk, limited transfer across placenta	Likely compatible
Natalizumab	C		

- Consider giving last dose of IFX around 30 weeks of gestation, then immediately after delivery.
- Consider giving last dose of ADA 6-8 weeks before delivery, then immediately after delivery.
- Continue certolizumab throughout pregnancy without interruption.

Pregnancy: Delivery concerns

- C-sections are more common in women with IBD.
- Consider a C-section in women with active perianal disease to minimize perineal and sphincter trauma.
- It is not clear whether vaginal delivery after IPAA affects sphincter function, so C-section should be considered in this case as well.

Pregnancy: Infant outcomes

- IFX and thiopurine levels are detectable in cord blood and serum of newborns
- Thiopurines are cleared more efficiently than IFX, but the duration of the effect of each on the infant's immune system is unknown
- No reported adverse events
- Avoid rotavirus vaccination with IFX and ADA
- Check titers at 7 months to confirm response to *H. influenzae* and tetanus toxoid in all infants exposed to anti-TNFs in utero

HRT and IBD

- No difference between disease activity in the pre- and postmenopausal states
- HRT may have a protective effect against disease flare during menopause
- This potential benefit must be weighed against increased breast cancer, coronary heart disease, and, thrombotic risk

Osteoporosis: risk in IBD

- Prevalence is similar to general population
- Fracture risk is 40% greater in IBD vs. the non-IBD population
- Risk factors include female gender, increasing age, low BMI, smoking, family history, vitamin D deficiency, corticosteroid use

Osteoporosis: Corticosteroid effect

- Corticosteroids negatively affect bone mass by various mechanisms
- Effects are thought to take place within weeks to months after initiation
- Even small doses are thought to adversely affect bone density

Osteoporosis: Prevention

- Smoking cessation
- Weight-bearing exercise
- Calcium (1000-1500mg daily) and vitamin D supplementation (400-800 IU daily)
- Treatment of vitamin D insufficiency/deficiency
- Avoid chronic corticosteroids

Osteoporosis: Diagnosis and treatment

- DXA scan
 - 1+ risk factors: baseline and q2-3y
 - If steroid use, annual screening
- Follow all prevention measures
- Consider bisphosphonates in osteoporosis, atraumatic fracture, and corticosteroid use >3 months

Conclusions

- Gender differences in clinical course
 - Female patients with IBD are more likely to have EIM, and may have a more severe disease course.
- Influence of menstruation and IBS
 - Women may experience GI symptoms before and during menses that mimic active IBD.
 - IBS-type symptoms in IBD patients may indicate occult inflammation or coexistent IBS.
- Body image and sexual dysfunction
 - IBD significantly affects body image and sexual function in women, which have profound effects on quality of life and emotional health.

Conclusions

- Contraception
 - Pregnancy in IBD should be a planned event.
 - Avoid OCP in smokers, hypercoagulability.
- Cervical dysplasia
 - Women with IBD on immune suppression should have annual Pap smears.
 - Consider HPV vaccine in female patients age 9-26.
- Fertility
 - Women with IBD have similar rates of fertility to the general population.
 - Increased rates of infertility are seen in women with UC who undergo IPAA

Conclusions

- Pregnancy and breastfeeding
 - Consider consultation with a high-risk obstetrician.
 - The goals during pregnancy in IBD are to maintain the health of the mother while minimizing risk to the fetus.
 - Methotrexate and thalidomide are contraindicated in pregnancy and breastfeeding.
 - Thiopurines and anti-TNF therapy should be continued.
 - Consider C-section in patients with active perianal disease or s/p IPAA.
 - Infants born to mothers on anti-TNF agents or thiopurines should not receive live vaccines for the first 12 months of life.

Conclusions

- Hormone replacement therapy and osteoporosis
 - HRT may improve disease course in postmenopausal women with IBD, but significant adverse effects restrict its use.
 - Women with IBD and risk factors for osteoporosis should undergo routine screening with DXA.
 - Preventive measures against osteoporosis, including calcium and vitamin D supplementation and avoidance of long-term steroids, should be utilized in women with IBD.

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