Managing Inflammatory Bowel Disease Through Childbearing Years

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Topics for Discussion

• OCP/Hormones
• Natural History Considerations
• Treatment Considerations
• Pregnancy
  – Role of Inflammation
  – C section vs vaginal delivery
OCP and the Risk of Crohn’s


OCP and IBD

- Nurses Health Study I and II used
- HR for CD was 2.82 (1.65-4.82) among current users and 1.39 (1.05-1.85) former
- For UC HR in smokers 1.63 (1.13-2.35)

OCP and Antibiotics

- Common misperception about decreased efficacy of antibiotics with OCP
- Based on old data of rifampin clearance
- Pharmacokinetic data for PCN derivatives, metronidazole, quinolones do not suggest such an effect
- ACOG guidelines 2006 state no interaction

Flynn A. Am J Gastroenterol 2011; 106(6):1174-5.

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Disease Course and Gender

• Cumulative 10 yr relapse rate in UC
• 771 patients from 8 countries (European Collaborative Study Group of IBD)
• HR for time to first relapse for women was 1.2 (1.0-1.5)
• Relapse rate was 1.2 times higher in women than in men


IBD and Menstrual Cycle

• Mailed survey of 151 IBD vs 156 controls
• Premenstrually and during menses diarrhea reported more often in CD (48%, 60%) than UC or controls
• Premenstrually CD more likely to report worsening of IBD symptoms (46%) vs UC (26%) but not during menses

Bernstein MT. Aliment Pharmacol Thera 2012; 36:135-144.
Hormone Fluctuation and Symptom Severity

- 1203 patients from CCFA Partners database surveyed
- 53% CD, 51% UC endorsed worsening symptoms during menses
  – tended to be younger and had worse QoL scores
- 10% had improved sx on OCP, 7.5% had worse sx

Boroujerdi L. Gastroenterol 2013; Mo1306 [Abstract]

Menstrual Function in IBD

- Incident cases of IBD from OSCCAR interviewed about menstrual symptoms
- In UC, higher disease activity associated with longer cycle length and pain
- In CD, higher disease activity associated with longer length of pain
- Steroids associated with irregular cycles

Saha S. Inflamm Bowel Dis 2014
Endometriosis Increases Risk of IBD

- Nationwide Danish study 37,661 pts
- Risk of IBD SIR 1.5 (1.4-1.7)
- Those with surgically verified endometriosis SIR 1.8 (1.4-2.3)
- Is it that there is a common immunologic component, or impact of OCP treatment of endometriosis?

Endometriosis

- Can mimic IBD
- Clinical observation: women with concurrent endometriosis have more refractory disease
  - Require biologics earlier
  - Dose escalation more frequently
- Increased number of activated macrophages in pelvis/abdomen that potentiates increased expression of pro-inflammatory cytokines
Ovarian Cysts

- CCF study: 39% of women with IBD had ovarian cysts, over half required surgery for such.
- UCLA: Presence of large ovarian cysts (LOC, > 5 cm) led to increased risk of post-op complications.
- UK: LOC associated with more aggressive disease, more steroid exposure.


Incidence of Abnormal Pap Smears in IBD

- Abnormal Pap smears associated with both infection and progression to cancer.
- Incidence study of women with IBD and a history of abnormal Pap smears.
- Adjusted for smoking, OCP use and parity.
- Women with IBD were more likely to have an abnormal Pap.
- Use of azathioprine increased risk 3 fold.

More Data on Cervical Cytology

- UNC: women with IBD get more Paps than healthy population
- Northern Scotland: No increased risk for abnormal cytology in women with IBD, no account for medication exposure
- Manitoba: No increased risk for abnormal cytology, although timing of immunosuppressants unclear

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Clearance of biologics

- Two studies suggest that clearance of mAbs is higher in men
- Influence of weight on clearance is not linear; weight and sex are somewhat correlated clinically
- Unclear if sex alone a factor


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  - C-section vs vaginal birth
Ovarian Reserve in CD

- Anti-Müllerian hormone (AMH) is a marker of fertility (ovarian reserve)
- 50 CD in remission vs. 163 controls
- In patients > 30, AMH lower in CD 49 vs 24%, p=0.002
- Colonic location OR 5.59 (.13-27.6) for lower level

Freour T. *Inflamm Bowel Dis* 2012; 18(8):1515-1522

Cytokine spectrum in Pregnancy

- Early: dominant proinflammatory profile
  - Embryo invades and damages maternal uterus to implant
- Middle:
  - Decrease in proinflammatory cytokines. Mother, fetus, placenta in synchrony
- Late:
  - Increase in proinflammatory cytokines to activate parturition
Effect of Cytokines on Pregnancy Outcome

- Circulating levels of TNFα, IFNγ and IL-6 and -10 measured in women with threatened miscarriage
- Those women who subsequently miscarried had significantly higher levels of TNFα, TNFα/IL-6 ratio than women who were able to carry to term


Effect of Cytokines on Birth Outcomes

- Serum from pregnant women collected and titers for INFγ, IL-2,-7,-10,-12 measured at gestation weeks 7-10
- Outcomes of pregnancies documented
- Those women with high circulating levels of INFγ, IL-2,-7 and -12 and lower IL-10 had babies with SGA (p < 0.03)

Does Having a C-section increase Risk of Developing IBD?

- CS disturbs normal bacterial colonization of newborn’s intestine\(^1\)
- Swedish Case-Control study 1536 cases\(^2\)
  - CS increased risk of pediatric CD among boys (OR = 1.25, 95% CI 1.01-1.54) but not girls, (OR = 0.99, 95% CI 0.76-1.29)
- Danish Population Based study\(^3\)
  - 32.6 million person-years of follow-up
  - CS increased risk of IBD at age 0-14 years (IRR 1.29, 95% CI 1.11-1.49)
  - Assuming causality, an estimated 3.2% of IBD cases before age 15 years were attributable to cesarean section
- Henderson: increase in IBD risk nearly boys\(^4\)
  - IRR=1.26 (1.15,1.37) vs. 1.06 (1.15 among girls)
  - Higher for UC than CD


Summary

- Hormones play a role in pathogenesis, disease course, complications
- Conditions unique to women can mimic IBD and should be considered in Ddx
- Inflammation is bad