Gender Related Issues in the Female with IBD

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Topics for Discussion

• Natural History
  – Disease course
  – Effect of Smoking
  – Role of hormones
• HPV and Pap smears
• Pregnancy
  – Outcomes
  – Placental physiology
  – Nursing
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

The Effect of Smoking on Crohn’s Disease in Women

• There are now two studies that have specifically addressed the gender effect of tobacco
• Women smokers undergoing surgery are 5 times more likely to have a recurrence than a non-smoker, and recur more quickly\(^1\)
• Women smokers hastened onset of disease and increased the need for immunomodulators\(^2\)

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 2 years post menopause
• Dose response for length of use
• Form of menopause did not matter

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

9657 women 14-65 undergoing routine Pap screening in 6 US cities

Overall high risk HPV by Hybrid Capture testing was 23% (22% -24%

Prevalence highest in women 14-19 (35%)

Women with an abnl Pap had a prevalence of 53%

HPV Vaccines

• Gardasil currently approved for 9-26 yrs
• Data submitted to FDA for 27-45
• Covers HPV 6,11,16,18
• Cervarix by GSK 10-55 before FDA
HPV Vaccine

• L1 major capsid protein of HPV in S. cerevisiae
• Protective for HPV stains 6, 11, 16, 18
• Advisory Committee on Immunization Practices:
  age 11-12 with 3 doses, early as age 9, up to 26
• ACOG: ages 9-26
• ACS: no older than 18 since HPV exposure has already occurred
• Need to know: duration of protection
  effect on prevalence of HPV types
  safety, immunogenicity
In-hospital Management and Birth Outcomes

- 18 cases, 41 controls from 2 tertiary centers
- Median GA at hospitalization 15.9 wk (5-35)
- LOS 10.4 days (3-31)
- 18 IV steroids, 5 CsA, 3 AZA, 3 colectomy
- Delivery at 35 weeks vs. 38.7 for controls
- 0 stillbirths, congenital abnl, 1 spon Ab
- Birth wt 2000g vs. 3000 g, APGAR scores similar

Immune System Development

- 19 infants born to mothers on CS alone or with AZA, CsA or HCQ compared to 15 infants born to normal mothers
- *No mothers with IBD studied*
- Mean CS dose 8.7 mg/day
- No differences in:
  - Absolute lymphocyte count
  - % circulating lymphocyte subsets
  - Immunoglobulin production

Means of Placental Transfer

- Simple diffusion (most drugs pass this way)
- Solvent drag
- Transcellular transfer
  - Channels
  - Facilitated diffusion
  - Carrier mediated active transport
- Endo- and exocytosis
Placental IgG transport

IgG Placental Transport Over Time

Placental IgG Transport

• Hierarchy for transport:

IgG1 >> IgG3 > IgG2 > IgG4
• ReoPro, an Fab’ fragment used for inhibition of platelet aggregation, has not been found in fetal circulation
• Was found to be attached to maternal and fetal platelets, but “no clinical consequence”

Pegol

- In animals, PEG is cleaved and cleared through the urine
- No human studies have investigated the elimination of PEG derived specifically from certolizumab pegol
## Infliximab Levels in Infants

<table>
<thead>
<tr>
<th>#</th>
<th>M pre-birth INF level</th>
<th>Time infusio n and birth (days)</th>
<th>M INF at birth</th>
<th>Cord blood INF level</th>
<th>N INF level at birth</th>
<th>Month level undetectable</th>
<th>M complications</th>
<th>N complications</th>
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<td>21.3</td>
<td>30</td>
<td>15.1</td>
<td>--</td>
<td>25.3</td>
<td>5</td>
<td>Pernie al tear</td>
<td>Meconium</td>
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<tr>
<td>2</td>
<td>2.0</td>
<td>2</td>
<td>1.4</td>
<td>2.0</td>
<td>--</td>
<td>2</td>
<td>Perine al tear</td>
<td>Hand-foot-mouth</td>
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<tr>
<td>3</td>
<td>8.3</td>
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<td>19.2</td>
<td>26.5</td>
<td>23.6</td>
<td>5</td>
<td>Candid a on breast</td>
<td>Oral candid a</td>
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<tr>
<td>4</td>
<td>5.7</td>
<td>91</td>
<td>3.8</td>
<td>3.3</td>
<td>4.2</td>
<td>2</td>
<td>Jaundi ce</td>
<td></td>
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<tr>
<td>5</td>
<td>--</td>
<td>15</td>
<td>--</td>
<td>--</td>
<td>39.5</td>
<td>6</td>
<td>None</td>
<td>None</td>
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</tbody>
</table>

Mahadevan U. Gastro 2007; 132(4)Suppl 2 A-144
Neonatal Immune Response

- 8 mothers receiving infliximab during third trimester of pregnancy
- All infants had appropriate IgG, IgA levels
- Levels of IgM low in 4/6
- 8/8 converted tetanus
- 7/8 converted Hib

# Postpartum Infliximab and Breast milk

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<th>Subject</th>
<th>Sample</th>
<th>Days post IFX</th>
<th>Sample collected</th>
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Kane SV. *J Clin Gastro* 2008 (in press)
Azathioprine During Nursing

- 8 lactating women on 75-200 mg studied
- Milk and plasma collected 30,60 mins and hourly x 5; drug taken in am
- Highest concentrations excreted within first 4 hours after drug intake
- Worst case scenario infant receives 0.0075 mg/kg bodyweight (less than 1% of maternal dose)

Christensen LA. *Aliment Pharmacol Thera* [Epub ahead of print 2008]