Management of IBD in Pregnancy

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Today’s Topics

• Fertility
• Effect of pregnancy on IBD
• Management of IBD during pregnancy:
  – Medications during pregnancy
  – Breastfeeding considerations
  – Mode of delivery
Pre-pregnancy Counseling

• Document the time spent with patient
• You CAN bill for a visit for this:
  – V25.09 (search under “pre-pregnancy counseling” or “family planning”)

Definitions

• Fecundity:
  – the ability to have children
  – fecundation - aka fertilization (natural or IVF)
• Fertility:
  – the ability to conceive & become pregnant through normal sexual activity
• Infertility:
  – failure to conceive s/p 1 yr of intercourse
  – background rate – 1 in 7 couples (14%)
Infertility and IPAA

- Meta analysis regarding risk of infertility
  - Eight studies included in analysis
  - RR of infertility for medically treated UC was 15%, and 48% after IPAA
  - There were no procedural factors identified that consistently affected risk

- Colectomy with ileorectal anastomosis preserves female fertility


Effect of Pregnancy on IBD: Disease Activity at Conception

<table>
<thead>
<tr>
<th>Inactive</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=186</td>
<td>n=93</td>
</tr>
<tr>
<td>No Relapse</td>
<td>73%</td>
</tr>
<tr>
<td>Relapse</td>
<td>27%</td>
</tr>
<tr>
<td>Worsened Activity</td>
<td>34%</td>
</tr>
<tr>
<td>Continued Activity</td>
<td>32%</td>
</tr>
<tr>
<td>Decreased Activity</td>
<td>34%</td>
</tr>
</tbody>
</table>

Effect of Elevated CRP on Pregnancy Outcomes

- 8000 women being followed as part of Generation R Study—outcomes in women in Rotterdam
- CRP measured in early pregnancy in 6016 women, fetal growth in each trimester and neonatal outcomes studied
- Elevated CRP > 25 mg/L was associated with lower fetal weight in 3rd trimester, lower birth weight and SGA (2.94 [1.61-5.36])


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)


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**IBD and Pregnancy Outcomes**

Recent meta-analysis: 12 studies from 1986-2005
3907 patients and 320,531 population controls

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW</td>
<td>2.10</td>
<td>(1.38-3.19)*</td>
</tr>
<tr>
<td>Premature</td>
<td>1.74</td>
<td>(1.14-2.65)**</td>
</tr>
<tr>
<td>C section</td>
<td>1.58</td>
<td>(1.35-1.84)**</td>
</tr>
</tbody>
</table>

*Effect all from Crohn’s, no increased risk for UC
**Consistent findings through sensitivity analysis

Effect of Crohn’s on Pregnancy

- Population based prevalence study from Sweden and Denmark
- 2377 women with CD vs. 869,202 without CD
- No increased risk for congenital abnormalities noted
- Risk for birth outcomes higher with h/o maternal surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mod preterm</td>
<td>1.76</td>
<td>1.51-2.05</td>
</tr>
<tr>
<td>Very preterm</td>
<td>1.86</td>
<td>1.38-2.52</td>
</tr>
<tr>
<td>SGA</td>
<td>1.22</td>
<td>1.00-1.49</td>
</tr>
<tr>
<td>C-section</td>
<td>1.93</td>
<td>1.76-2.12</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0.73</td>
<td>0.30-1.76</td>
</tr>
<tr>
<td>Con Abnl</td>
<td>1.01</td>
<td>0.79-1.29</td>
</tr>
</tbody>
</table>


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

Outcomes of Obstetric Hospitalizations

- 2005 Nationwide Inpatient Sample
- 2372 CD and 1368 UC deliveries
- C section rate: CD 1.72 (1.44-2.04) UC 1.29 (1.01-1.66)
- VTE CD 6.12 (2.91-12.9) UC 8.44 (3.71-19.2)
- Malnutrition more likely OR 20, 60
- No other outcomes higher

<table>
<thead>
<tr>
<th></th>
<th>Non IBD</th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Csection</td>
<td>30.9%</td>
<td>45.9%</td>
<td>41.6%</td>
</tr>
<tr>
<td>Preterm</td>
<td>7.5%</td>
<td>11.4%</td>
<td>16%</td>
</tr>
<tr>
<td>VTE</td>
<td>0.2%</td>
<td>1.5%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>0.05%</td>
<td>1.3%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>


Update on PIANO

521 women enrolled, 353 completed pregnancy, 339 live births. No difference in rate of CA by drug exposure

<table>
<thead>
<tr>
<th></th>
<th>Month 4</th>
<th>Month 9</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td>89 (92.8%)</td>
<td>69 (90.6%)</td>
<td>56 (86.1%)</td>
</tr>
<tr>
<td>Group A</td>
<td>53 (93.2%)</td>
<td>41 (82.3%)*</td>
<td>33 (84.2%)</td>
</tr>
<tr>
<td>Group B</td>
<td>88 (94.8%)</td>
<td>60 (91.3%)</td>
<td>39 (89.6%)</td>
</tr>
</tbody>
</table>

*P = 0.04

Mahadevan U. Gastroenterol 2010 A;764.
Assessment of Disease Activity

- Laboratory studies (ESR, CRP, Hgb)
- Ultrasound – safe but impractical
- Low dose x-rays pose minimal fetal risk
- MR low risk if gadolinium not given
- Endoscopy – safe if for appropriate indication


Antenatal Adherence in Crohn’s Disease

- 132 Danish women with Crohn’s disease who gave birth 2000-2005
- Questionnaires sent to measure adherence before and during pregnancy
- 80% completion rate, adherence was 72% as measured by the Danish Prescription Database
- Those nonadherent because of fear of effects on fetus
- Smokers more nonadherent OR 3.41 (0.8-14.7)

Adherence During Pregnancy Associated with Pre-Pregnancy Counseling

- Retrospective survey study Danish study
- Women with UC surveyed re medication use during pregnancy
- 68% took medicines during pregnancy
- 80% less likely to be non-adherent during pregnancy if received counseling
- 40% had a flare of disease during pregnancy, only a third were non-adherent

Julsgaard M. Inflamm Bowel Dis 2011; 17(7):1573-80.

Phthalate Exposure

- Low molecular weight phthalate (diethyl phthalate [DBP]) used as a coating for oral medications
- Present on Asacol, Videx, Prilosec as well as other generics of omeprazole, Theo-Dur
- Linked to AE in animals
- Urinary levels 50 times that of normal population but have yet to be of consequence

Hernandez-Diaz S. Environmental Health Perspectives 2009; 117(2):185-89.
Medications: Steroids

- Increased spontaneous AB, stillbirth in *mice*
- Cleft palate seen in asthmatics
- No fetal adrenocortical insufficiency
- No effect on neonatal T cell function
- Prednisolone more efficiently metabolized by placenta than other steroids

Pregnancy Outcome in Inflammatory Bowel Disease for Women Treated with Thiopurine: Cohort from the CESAME Study

- 215 pregnancies (204 women) in the CESAME cohort 3/04 - 12/07
- 3 exposure groups compared:
  - TP (TP only or associated with another treatment: 5-ASA, CS or anti-TNF)
  - A drug other than TP
  - No medication

**Conclusions**
- TP use is not associated with increased risk of congenital abnormalities
- Increased incidence of LBW and prematurity under TP was not significant and may correlate to the underlying disease

Coelho J. Gut 2011; 60(2):198-203.
Physicians Comfortable Giving 6MP in Pregnancy

- Web based cross sectional survey study
- Among 175 questionnaires received, 89% continue azathioprine until delivery
- Those following > 100 patients more likely to recommend continuation


IgG Placental Transport Over Time

Cord Blood Infliximab Levels Higher than Maternal Despite Cessation Prior to Delivery


Minimal Transfer of Certolizumab to Newborn

Data courtesy of Dr. Uma Mahadevan
Lack of Placental Transfer of Certolizumab pegol

- In vitro perfused human term placentas used to measure antibody levels
- Levels in maternal circuit 100-200 mcg/mL
- At all time points (avg 5 hours) levels in the fetal circuit non-detectable
- Control IgG levels detected at 2 hours

Porter C. Gastroenterol 2010; A:W1208.

Mode of Delivery

- Multiple studies indicate elevated incidence of C sections in women with IBD
- Vaginal delivery usually safe for women with inactive perianal symptoms
- Vaginal delivery with episiotomy can be risk factor for perineal complications

Nursing and Disease Activity

- Questionnaire study from U of Manitoba IBD Research Registry
- 64.7% response rate
- 83.3% IBD patients nursed vs. 77.1% of general population ($p > 0.05$)
- Rate of disease flare similar in both groups OR 0.58 (0.24-1.43)


Budesonide and Nursing

- Milk and plasma levels obtained from 8 mother-child pairs for mothers on inhaled budesonide
- Concentrations in milk less than half in maternal plasma, ie passive diffusion
- Daily infant dose 0.3% of maternal dose plasma concentration 1/600th of that in maternal plasma assuming complete infant oral bioavailability

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)


Adalimumab and Nursing

- Blood, breast milk obtained every 2 days for 8 days after ADA 40 mg
- ADA measured by ELISA
- Serum levels rose to 4300 ng/ml
- Milk level 31 ng/ml on day 6

Ben-Horin S. *Clin Gastro and Hepatol* 2010;8(5):475-76.
Herbal Therapies and Nursing

- Fenugreek is an herbal supplement used by Asian-Indian women for centuries to increase milk production
- Popular with certain lactation experts
- Causes rectal bleeding—mechanism thought to be related to its warfarin-like components

IBD Management During Pregnancy

- Pregnancy outcomes best if patient in remission at time of conception
- Establish remission quickly
- Many therapies low risk during pregnancy
- Monitor fetal growth
- May need additional nutritional therapy because of drugs, malabsorption