ACG International Webinar Series:
Clinical Pearls for the Management of Pregnancy in IBD
Hosted by the South African Gastroenterology Society (SAGES)

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Mayo Clinic
Rochester, MN
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Senior Lecturer
University of Cape Town, South Africa
President, South African Gastroenterology Society
IBD Lead, Gastrointestinal Foundation of Sub-Saharan Africa

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Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

Clinical Pearls for the Management of Pregnancy in IBD

Sunanda Kane, MD MSPH FACG
Mayo Clinic Rochester
Topics

- COVID and pregnancy
- Fertility
- Disease management
- Mode of Delivery
- Pregnancy Outcomes

COVID and Pregnancy

- Gestational rhinitis, due to estrogen-mediated hyperemia of the nasopharynx, usually affects one-fifth of healthy women in late pregnancy and results in marked nasal congestion and rhinorrhea
- Functional residual capacity, end-expiratory volumes, and residual volumes decrease steadily from early pregnancy due to diaphragmatic splinting by the gravid uterus, resulting in reduced total lung capacity at term and an inability to clear pulmonary secretions effectively
- Fetal complications of COVID-19 include miscarriage (2%), intrauterine growth restriction (IUGR; 10%), and preterm birth (39%)
- Remdesivir use appears to be safe in human pregnancies
- Vaccination recommended for all pregnant women

Fertility Concerns

• No surgery and in remission fertility rates equal to background population
• Active disease has been associated with decreased fertility
• Voluntary childlessness rate high (17% vs 6%)
• ART not as successful in IBD, likely from lesser change of achieving a chemical pregnancy

Delayed Time to Conception

• Danish National Birth Cohort, 92,274 pregnant women 1996-2002
• Women who had been actively trying to conceive reported time to pregnancy when approx 16 wks of gestation
• Calculated time to pregnancy for 74,471 pregnancies in women without IBD, 340 pregnancies in women with UC, and 206 pregnancies in women with CD
• Compared to non-IBD pregnancies, the adjusted RR for time to pregnancy of > 12 months in women with IBD, UC, and CD were 1.28 (95% CI, 0.99–1.65), 1.10 (95% CI, 0.80–1.51), and 1.54 (95% CI, 1.03–2.30), respectively
• The adjusted RR was 2.54 (95% CI, 1.39-4.65) for a time to pregnancy of more than 12 months in women who had CD surgery prior to conception vs non-IBD pregnancies (too few patients with UC with surgery prior to conception to perform meaningful analyses of this group)

Friedman S. Clinical Gastroenterology and Hepatology 2020;18:1537–1544
Adalimumab and Infertility

- Women with sub-fertility and Th1/Th2 cytokine elevation were treated with IVIG ± adalimumab
- 74 patients < 38 yrs old were allocated to one of four groups
- Women given ADA did better than those who got nothing or IVIG

<table>
<thead>
<tr>
<th></th>
<th>Implantation (%)</th>
<th>Pregnancy (%)</th>
<th>Live birthrate (%)</th>
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</thead>
<tbody>
<tr>
<td>ADA + IVIG</td>
<td>59</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>IVIG</td>
<td>47</td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td>ADA</td>
<td>31</td>
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<tr>
<td>None</td>
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</table>


Clinical Care Pathway

- Multi-disciplinary work group of gastroenterologists, maternal fetal medicine specialists, teratologists, lactation specialists and patient stakeholders
- In conjunction with AGA and CCF
- Published simultaneously in Gastro, Am J OB/Gyne, and IBD journal


American College of Gastroenterology
Disease Management

• Start a prenatal vitamin sooner vs later
• Steroids are not a maintenance medication!
• Stability on drug regimen for 3 months
• Dosing of weight based on pre-pregnancy wt
• Check a drug level at conception
• Consider second trimester drug level
• Tofa washout of 1 week before conception

Effect of Active IBD on Pregnancy

• 2008-14 pregnancies in Rotterdam followed prospectively, 298 in 229 IBD patients
• 226 live births recorded, 9 birth defects
• Active disease at conception associated with disease relapse during pregnancy with aOR 7.66 (3.77-15.54)
• UC patients experienced relapse more often than CD, OR 3.71 (1.86-7.4)
• Active disease in nulliparous women lead to more spontaneous abortion and LBW

De lima-Karagiannis A. Am J Gastroenterol 2016; 111:1305-1312.
Risk of Adverse Pregnancy-related Outcomes

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IDP pregnancy</th>
<th>Non-IDP pregnancy</th>
<th>Odds ratio</th>
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<tr>
<td>Bunker 2007</td>
<td>196</td>
<td>869</td>
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<td>1.46</td>
<td>[1.32, 2.63]</td>
<td>1.28</td>
<td>0.85</td>
<td>[0.57, 1.31]</td>
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<td>D'Amico 2006</td>
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<td>1.38</td>
<td>[0.92, 2.03]</td>
<td>1.16</td>
<td>0.74</td>
<td>[0.48, 2.31]</td>
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<tr>
<td>Italy 2005</td>
<td>21</td>
<td>114</td>
<td>2.94</td>
<td>2.29</td>
<td>[0.85, 6.52]</td>
<td>1.42</td>
<td>0.95</td>
<td>[0.57, 2.73]</td>
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<tr>
<td>Lubrothall 2009</td>
<td>17</td>
<td>152</td>
<td>2.17</td>
<td>1.20</td>
<td>[0.63, 2.39]</td>
<td>0.91</td>
<td>0.60</td>
<td>[0.37, 2.00]</td>
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<tr>
<td>Oson 2014</td>
<td>12</td>
<td>91</td>
<td>1.88</td>
<td>1.36</td>
<td>[0.73, 2.58]</td>
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<td>0.82</td>
<td>[0.53, 2.41]</td>
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<tr>
<td>Overall (18%)</td>
<td>132</td>
<td>1158</td>
<td>1.79</td>
<td>1.24</td>
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<tr>
<td>Total events</td>
<td>173</td>
<td></td>
<td></td>
<td></td>
<td></td>
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P<0.00001, P=0.83

Text for overall effect: Z=0.60 (P=0.545)

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<td>Pre-eczema</td>
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<td></td>
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Fecal Calpro in Pregnancy

- 219 singleton pregnancies in Denmark with moderate to severe disease
  - Inactive 80-120
  - Mild 259-349
  - Mod-severe 778-1277

- Sens 70-80%, spec 66.7-73.3% and PPV 66.7-74.4% when cut off of 200 used
Safety of Colonoscopy in IBD

- Case control of pregnant IBD patients matched to age, meds and disease activity
- 42 women underwent 47 lower GI procedures 2008-2014
- Median birthweight lower in cases but no difference in SA, gestational age, birth defects or APGAR scores


Corticosteroid Use during Pregnancy and Risk of Orofacial Clefts

- No statistically significant increased risk of orofacial clefts associated with the use of corticosteroids:
  - Cleft lip with/without cleft palate, OR 1.05 [0.80–1.38]
  - Cleft palate alone, OR 1.23 [0.83–1.82]
  - OR for cleft lip with or without cleft palate associated with the use of dermatologic corticosteroids was 1.45 [1.03–2.05]

Hviid et al CMAJ. 2011 April 19; 183(7): 796–804
Anti TNF Levels During Pregnancy Remain Stable

Flanagan E. DDW May 2020 Abstract 236

Continuous Use of Anti-TNF During Pregnancy

- French National Health System Database
- 1457 IBD pregnancies exposed to anti TNF
- Outcome a composite score of disease, treatment and pregnancy related complications
- aOR for a maternal complication 1.49 (1.31-1.67), infection 1.31 (1.16-1.97)
- No increased risk after 24 weeks for complication but stopping increased risk for disease flare
- No infection risk in infant to 1 yr
- Authors did not support stopping at beginning of third trimester

**Early vs Late Discontinuation IFX**

Early discontinue group:
- Required more steroid use
- More preterm deliveries in early
- Predicted flare (OR, 5.98; 95% CI, 1.83–19.5)

**Vedolizumab Levels During Pregnancy Remain Stable**

Infant:Maternal Ratio 0.6
Cleared by week 15

Flanagan E. DDW May 2020 Abstract 236
Ustekinumab in Pregnancy

- 206 reports available (164 PsO, 6PsA, 36 CD)

Tofacitinib in Pregnancy

- Data from 5 registration trials and post marketing reports
- 11 cases of maternal exposure
- 14 cases paternal
- 4/11 healthy newborns, 11/15 from males
- No neonatal deaths, congenital abnl
- 2 spontaneous Ab (both in women)
Delivery Plan

- CS for rectovaginal fistula, active p/a disease
- IPAA case by case basis, talk to the surgeon
- Vaginal delivery does not affect risk of development of IBD
- Dosing of biologic after delivery
- If CS then anticoagulation prophylaxis

FIGURE 1. Risk of relapse in women with inflammatory bowel disease in the postpartum year, stratified by therapy

Yu A. Inflammatory Bowel Diseases, 2020 https://doi.org/10.1093/ibd/izz313
Post-Delivery Care

- Dosing of weight based on pre-pregnancy wt
- Lactation Pearls
  - No tofa or MTX
  - Mesalamine over SASP
  - Thiopurines, biologics fine
  - Avoid fenugreek for milk stimulation
  - Pumping and dumping discouraged

Biologics in Breast Milk

<table>
<thead>
<tr>
<th>N</th>
<th>Agent</th>
<th>Max mcg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>19/29</td>
<td>IFX</td>
<td>0.74</td>
</tr>
<tr>
<td>2/21</td>
<td>ADA</td>
<td>0.71</td>
</tr>
<tr>
<td>3/13</td>
<td>CTZ</td>
<td>0.29</td>
</tr>
<tr>
<td>1 of 2</td>
<td>NAT</td>
<td>0.46</td>
</tr>
<tr>
<td>4/6</td>
<td>UST</td>
<td>1.57</td>
</tr>
<tr>
<td>0/1</td>
<td>GOL</td>
<td>--</td>
</tr>
</tbody>
</table>

- Milk collected hr 1,12,24,48 after dosing, up to 168 hrs
- Rates of infection and developmental milestones did not differ between breastfed vs not
- (39% in both)

Matro R. Gastroenterol 2018; Sep;155(3):696-704.
Meta Analysis of Neonatal Outcomes

Incidence of Adverse Neonatal Outcomes in Patients With Inflammatory Bowel Disease During Pregnancy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. Studies</th>
<th>No. Affected Pregnancies/Total No. Pregnancies</th>
<th>Incidence (%) 95% CI</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth</td>
<td>48</td>
<td>59/7017</td>
<td>8.6 (7.0-10.2)</td>
<td>53.3</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>29</td>
<td>190/14078</td>
<td>9.9 (7.3-10.5)</td>
<td>58.1</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>15</td>
<td>162/1398</td>
<td>5.2 (3.6-6.6)</td>
<td>31.2</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>45</td>
<td>386/6431</td>
<td>2.1 (1.6-2.6)</td>
<td>37.2</td>
</tr>
<tr>
<td>Neonatal intensive care unit admission</td>
<td>14</td>
<td>31/2431</td>
<td>4.5 (3.0-6.5)</td>
<td>82.8</td>
</tr>
</tbody>
</table>


Safety of first year vaccination in children born to mothers with IBD and exposed in utero to anti-TNFα agents: a French nationwide population-based cohort

47% had exposure throughout pregnancy

Luu M. Alimentary Pharmacology & Therapeutics 2019; 50, Issue: 11-12, Pages: 1181-1188.
Vaccines

• All given on scheduled EXCEPT
  – Live virus with in utero biologic exposure for 6 mo
• MMR and varicella are live but given at 1 year and are appropriate

Developmental Milestones

• Normal seen with TP, biologic exposure
• Ages and Stages questionnaire appropriate
• Effect of inflammation in utero on developing brain actively being studied
Pregnancy Onset IBD

- Pregnancy-onset IBD 2006-18 at 2 major academic referral centers
- 50 patients with pregnancy-onset IBD and 100 control patients matched for year of diagnosis. The mean age of diagnosis and duration of follow-up was similar among both patients and control patients (aged 30.4 vs 28.5 years)
- 30% noted symptom onset in the first trimester, 22% in the second, 24% in the third, and 24% in the postpartum year
- Patients with pregnancy-onset IBD were more likely to be diagnosed with ulcerative colitis compared with control patients (76% vs 56%; P = 0.02)
- On multivariable analysis, pregnancy onset-disease had a 4-fold increase in the risk of hospitalization (28% vs 13%; aOR ratio 4.18; 95% CI 1.26-13.91). Risk persisted even after excluding any index hospitalizations during pregnancy


IFX Use In A Pediatric Patient After In Utero Exposure

- Maternal use 10 mg/kg q 4-5 wks throughout pregnancy
- Healthy boy with no medical issues until 3 yo
- After 2 courses antibiotics developed diarrhea
- Diagnosed with Crohns colitis
- Age 14 started on IFX for refractory disease
- Continues on 10 mg/kg q 5 wks without antibodies out to age 17

Vedo Use During Pregnancy


Summary

- Infertility increased after surgery
  - Open > laparoscopic technique
  - ART is an effective option
- Active inflammation at conception is associated with infertility
- All women with IBD of reproductive age should receive preconception counseling to improve pregnancy outcomes
- Most medications are safe to continue in pregnancy and breastfeeding
  - Exceptions: methotrexate, certain antibiotics
- Disease flare poses a bigger threat to the health of Mom and Baby than biologics
- Mode of delivery should consider active perianal disease, sphincter preservation