IBD Treatment in Special Populations

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Disclosures

I have no financial relationships with any commercial interest related to the content of this activity
Objectives

- Review the effects of pregnancy on the course of IBD as well as how IBD affects fertility and fecundity.
- Provide framework for managing IBD during pregnancy and the postpartum phase.
- Examine the risks and benefits of IBD therapies when used in the elderly.

“All patients are special…but some are more special than others”
Peak IBD incidence occurs during child bearing years.

IBD course no different in pregnancy if patient is in remission at time of conception\(^1\).

IBD in pregnancy is associated with small increase in incidence of prematurity, low birth weight, likelihood of C-section and risk of congenital abnormalities\(^2\).

1. Mahadevan et al. Gastroenterology. 2007; 113: 1106–1112)
Preconception counseling is paramount!

- False beliefs regarding IBD and pregnancy are common in our patients\(^1,2\)

- Patients who receive preconception counseling have better outcomes\(^3\)

- IBD related risks for poor pregnancy outcomes is predominantly determined by disease activity at time of conception\(^4,5\)

1. Tavernier et al. Aliment Pharmacol Ther. 2013: 38; 847-853
2. Selinger et al. J of Crohn’s and Colitis. 2013: 7; 206-213
IBD and Pregnancy Patient Resources

AGA IBD Parenthood Project
ibdparenthoodproject.gastro.org

Crohn’s and Colitis Foundation
Pregnancy Fact Sheet
FDA PLLR for Medications

OLD SYSTEM
- Pregnancy Classes A, B, C, D and X

NEW SYSTEM
- FDA Pregnancy and Lactation Labeling Rule (June 30th, 2015)
- Narrative that summarizes risks and benefits of treatment during pregnancy and lactation
- June 2020 all old medications will have old system removed
Pregnancy Considerations

Prednisone and its metabolite, prednisolone, cross the placenta.

In the mother, prednisone is converted to the active metabolite prednisolone by the liver. Prior to reaching the fetus, prednisolone is converted by placental enzymes back to prednisone. As a result, the level of prednisone remaining in the maternal serum and reaching the fetus are similar; however, the amount of prednisolone reaching the fetus is ~8 to 10 times lower than the maternal serum concentration (healthy women at term) (Beitins 1972).

Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts or decreased birth weight; however, information is conflicting and may be influenced by maternal dose, duration/frequency of exposure, and indication for use (Lunghi 2010; Park-Wylie 2000; Pradat 2003). Hypoadrenalism may occur in newborns following maternal use of corticosteroids in pregnancy; monitor. An increased risk of adverse maternal outcomes, including gestational diabetes, may be associated with use of high doses over extended periods (Murase 2014; Rademaker 2018).

When systemic corticosteroids are needed in pregnancy for rheumatic disorders, it is generally recommended to use the lowest effective dose for the shortest duration of time, avoiding high doses during the first trimester (Götestam Skorpen 2016; Makol 2011; Østensen 2009).
5-ASAs and Pregnancy

Considered low risk for adverse outcomes with pregnancy\(^1\)

Sulfasalazine impairs folate absorption (recommend 2 mg/day supplementation)

Reports of enteric coated mesalamine with dibutyl phthalate (DBG) causing congenital malformations in animal models\(^2\)

*DBG formulations not commercially available in USA*

2. FDA Medication Safety
Corticosteroids and Pregnancy

Older studies reported small risk for cleft palate, but newer studies have not demonstrated this risk\(^1,2\)

Rare risk for fetal adrenal insufficiency at prolonged exposure to \(>20\text{mg per day}\)\(^3\)

Use in all indications you would in non-pregnant patient

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2. Hviid et al. CMAJ. 2011: 183; 796-804
3. JAMA. 1995: 273; 413
Immunomodulators and Pregnancy

Methotrexate
- Teratogenic
- Recommended to stop 3-6 months prior to conception (both males and females)

Thiopurines
- Several studies demonstrating low risk for adverse pregnancy outcomes $^{2,3}$
- Maternal metabolism of thiopurines altered during pregnancy$^4$

*consider checking TGN/6MMP metabolites if continuing maintenance*

IgG1 is actively transported across placenta during 3\textsuperscript{rd} trimester\textsuperscript{1}

- Infliximab, Adalimumab, Golimumab are all IgG1
- Certolizumab is Fab fragment (does not cross placenta)

Levels in fetal cord blood can be 4x higher than maternal blood and be detectable for up to 6 months\textsuperscript{1}

\textsuperscript{1} Mahadevan et al. Clin Gastroenterol Hepatol. 2013:11;286
Anti-TNF therapy and Pregnancy

Pregnancy in IBD and Neonatal Outcomes Registry (PIANO)\(^1\)

- N=1232 pregnant women (329 unexposed, 242 exposed to azathioprine, 357 exposed to biologic therapy, and 109 on combination biologic therapy and azathioprine during pregnancy)
- Anti-TNF monotherapy and combination therapy not associated with an increase in pregnancy complications or birth defects

Timing of last Dose?

- Treat through entire pregnancy, time last dose to have lowest level at due date, next dose 48hrs postpartum\(^2\)

1. Mahadevan et al. Gastroenterology. 2012: 14; S149
2. Mahadevan et al. Gastroenterology. 2019: 156; 1508-1524
Newer therapies and Pregnancy

**Ustekinumab**
- n=206 pregnancies from all sources, spontaneous abortion rate and congenital anomaly rate not different from general population\(^1\)

**Vedolizumab**
- No teratogenicity seen in animals, limited patient registry and trial data, but no evidence of adverse effects seen yet\(^2\)
- Technically not gut-selective (placenta blood vessels express MADCAM-1)\(^3\)

**Tofacitinib**
- Teratogenic in rabbits and mice at supratherapeutic doses, small sample size, n=33 in RA/PsA registries\(^4\)

“An ounce of prevention is worth a pound of cure”
• Preconception counseling and planning is best chance to modify risks of adverse pregnancy outcome

“What’s good for momma is good for baby”
• Most IBD medications are considered low risk in pregnancy and benefits of controlling disease outweigh risks of flare and the associated effects on pregnancy outcomes

Clinical Sources
• AGA Clinical Care Pathway: IBD in Pregnancy (2019)
• Toronto Consensus for Management of IBD in Pregnancy (2016)
# Maintenance Therapy in Pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Maintenance Dosing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA/Sulfasalazine</td>
<td>Maintain pre-pregnancy dosing (all preparations are phthalate-free)</td>
</tr>
<tr>
<td></td>
<td>2mg folate supp if on Sulfasalazine</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Contraindicated (stop 3 months prior to conception)</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>Continue as monotherapy. In low-risk patients consider cessation of thiopurine if on combination therapy</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Limited human data, consider other options (especially in 1\textsuperscript{st} trimester)</td>
</tr>
<tr>
<td>Biologics (anti-TNF safety data compelling, limited in VDZ and UST)</td>
<td>Maintain pre-pregnancy dosing and continue throughout all 3 trimesters</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Reserved for flares, not recommended as maintenance therapy</td>
</tr>
</tbody>
</table>

*Table modified from Toronto Consensus Statements*
Induction Therapy in Pregnancy

IBD and the Elderly

“Elderly” in the literature typically refers to over the age of 60 to 65.

Often studies do not distinguish between elderly-onset IBD and elderly patients who were diagnosed at a younger age.

Incidence of UC>CD, especially for males\(^1\)

30-35% of all IBD patients are >60 already\(^2\)

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IBD and the Elderly

Extent of disease is more limited in the elderly
• Colonic involvement in CD and left-sided UC are most common

Behavior seems to be more mild
• Stricturing and penetrating features less common in the elderly

Comorbidities and polypharmacy complicate care in elderly with IBD
• Avg of 10 medications in CD and 9 medications with UC

Increased risk of infectious complications and lymphoma related to age

4. SEER [Surveillance, epidemiology and end results] database
• Efficacy is the same as rest of general population with IBD$^1$

• Rectal therapy may be less well tolerated due to sphincter incompetence

• Half-life of 5-ASA can be increased in the elderly due decreased renal clearance$^2$
  - More frequent monitoring may be indicated in patients with reduced GFR

Response rates comparable to general population

- Short-term side effects: insomnia, mood instability, and delirium

Higher risk for serious adverse events with prolonged use

- Infections, metabolic derangements, osteoporosis related complications and ocular problems

Budesonide is an attractive option in the elderly

- $$ and insurance barriers

Methotrexate
• Increased risk of GI and myelotoxicity seen in RA literature¹

Thiopurines
• Increased risk of lymphoma, infection and NMSC
• Men > 60 highest risk for lymphoma
• Beware of allopurinol drug interaction
• Markov modeling study showed questionable benefit in QALY if used in age >65³

IBD and the Elderly: anti-TNF therapy

Equally efficacious in the elderly
• Multiple cohort studies (MGH, Mayo, Belgium) show that anti-TNF may be slower onset to response and elderly patients are more likely to discontinue therapy compared with younger patients\(^1\,2,3\)

Risk of severe adverse events higher in patients over 65
• RR 4.7 for both malignancy and infections\(^3\)

Combination therapy only in highly selected patients

2. Desai et al. Inflamm Bowel Dis. 2013: 19; 309–15
3. Lobaton et al. Aliment Pharmacol Ther. 2015: 42; 441–51
Excellent safety profile

- 1 yr retrospective multicenter cohort study showed similar effectiveness and safety for anti-TNF vs Vedolizumab in elderly patients

- VARSITY trial showed superiority of VDZ compared to ADA for biologic naïve patients with UC (included patients up to age 85)

Could make compelling argument for first line therapy for moderate to severe IBD in the elderly

2. Sands et al. NEJM. 2019: 381; 1215-1226
IBD and the Elderly: Ustekinumab

Infection and malignancy risk seems low based on clinical trial and registry data\(^1,2\)

- Safety data is lacking for elderly in IBD, PsA literature limited to small numbers and dosing is significantly lower

Most likely a safe option for the elderly, but insufficient data

IBD and the Elderly: Tofacitinib

Black Box Warning for 10mg BID dosing
- Risk of DVT/PE and mortality seen in RA pts aged >50 with at least one CV risk factor\(^1\)... not seen in IBD data

Increased risk of infections, especially herpes zoster

NMSC risk maybe confounded by thiopurine exposure

Lipids elevation
- Registry and post marketing data in RA/PsA has not shown increased major cardiac events\(^2\)

1. FDA.gov
IBD and the Elderly: Take Home Message

Elderly onset IBD tends to be more mild

IBD medications work just as well in the elderly, however they are at increased risk of AE’s and must weigh benefits vs risks

Be a good geriatrician

- Monitor for drug-drug interactions and polypharmacy
- Vaccinate (VZV, pneumonia and Flu)
Recommended Resources

AGA IBD in Pregnancy Clinical Care Pathway (2019)
  • LINK

Toronto Consensus Statements on Management of IBD in Pregnancy (2016)
  • LINK

  • LINK