IBD and Pregnancy: Optimizing Care of Mother and Baby

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@DCharabaty
@MondayNightIBD
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Relevant Disclosures

- Advisory Board/Consulting – AbbVie, Takeda, Janssen, Pfizer, BMS,Eli Lilly
- Founder – @MondayNightIBD

Learning Objectives

- Understand the importance of preconception counseling
- Recognize the safety of IBD therapies during pregnancy and breastfeeding
- Manage a flare during pregnancy

IBD = inflammatory bowel disease.

Overview

- 3.1 million adults in the US diagnosed with IBD
- Peak incidence during prime child-bearing years

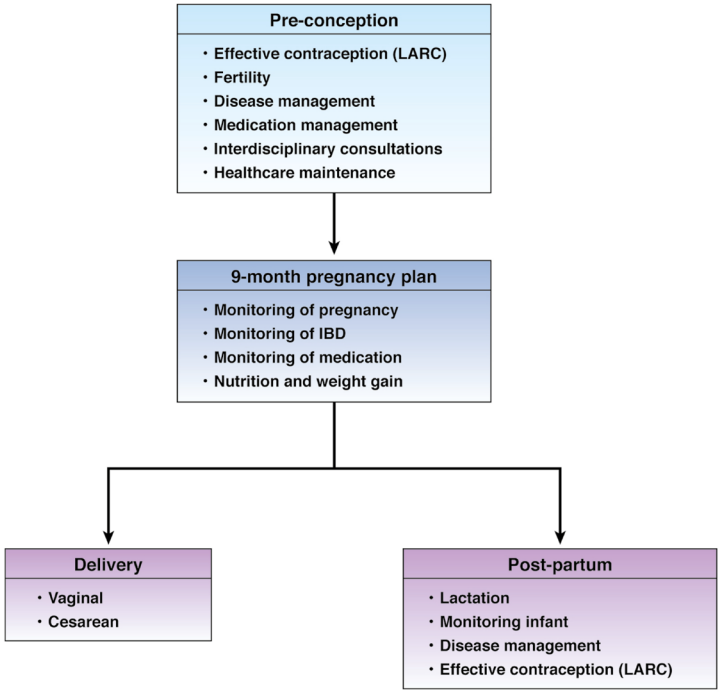
- Concerns about effects of disease and medications on fertility, pregnancy, delivery, breastfeeding, and infant health and development

Key Messages

- Healthy mom = healthy pregnancy = healthy baby
- For the most part: Treat the pregnant person similar to non-pregnant person
- Plan ahead: Start counseling before pregnancy

CDC. Accessed July 12, 2022. https://www.cdc.gov/ibd/features/IBD-more-chronic-diseases.html.

AGA Institute Guideline on IBD in Pregnancy
Clinical Decision Support Tool



Overview of IBD in pregnancy clinical care pathway

AGA = American Gastroenterological Association; LARC = long-acting, reversible contraception.

Mahadevan U et al. *Gastroenterology*. 2019;156(5):1508-1524.

Fertility

- Fertility rate in ♀ with IBD = age-matched control

- Voluntary childlessness
  - Sexual dysfunction (depression, low libido, dyspareunia)
  - Fear of intimacy, poor body image (ostomy, perianal disease)
  - Fear of IBD in offspring

Hudson M et al. *Int J Gynaecol Obstet*. 1997;58(2):229-237.

Factors That Affect Fertility

- Active disease
- Male infertility
  - Sulfasalazine: Reversible oligospermia, reduced sperm motility, abnormal sperm morphology
  - Methotrexate: Reversible oligospermia

- Total proctocolectomy with ileal-pouch anal anastomosis (IPAA)
  - Infertility up to 40% in women (pelvic adhesions and fallopian tubes scarring)
  - Discuss options with patients
    - Laparoscopic surgery: 1-year pregnancy rate – laparoscopic 56% vs > open 30%
    - Colectomy and end-ileostomy
    - Assisted reproductive techniques

Olsen KO et al. *Gastroenterology*. 2002;122(1):15-19; Timmer A et al. *Clin Gastroenterol Hepatol*. 2007;5(1):87-94; Beyer-Berjot L et al. *Ann Surg*. 2013;258(2):275-282.

Risk of IBD in Offspring

- Highest risk factor for IBD is FH +
  - But multifactorial disease, environmental factors

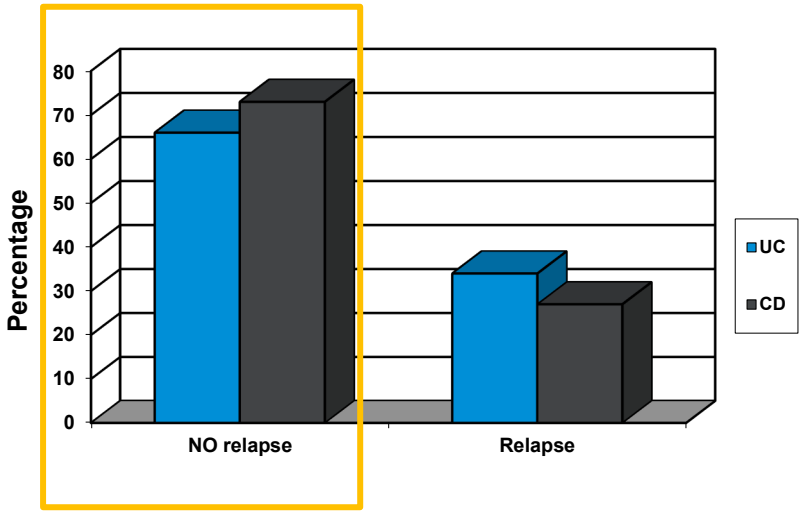
- Lifetime risk of developing IBD
  - One parent with CD: 5-10%
  - One parent with UC: 2-4%
  - Jewish families > non-Jewish families
  - Both parents with IBD: Up to 37%

FH = family history; CD = Crohn's disease; UC = ulcerative colitis.

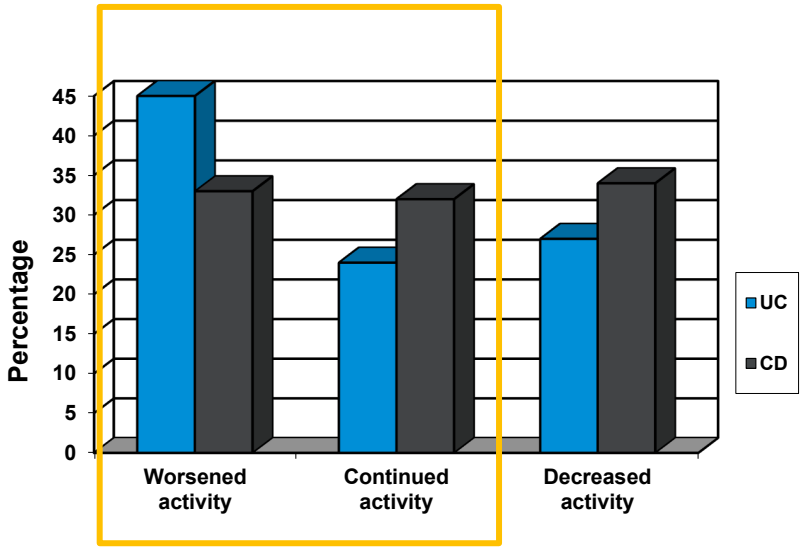
Yang H et al. *Gut*. 1993;34(4):517-524; Bennett RA et al. *Gastroenterology*. 1991;100(6):1638-1643.

Effect of Pregnancy on IBD

Inactive IBD



Active IBD



Abhyankar A et al. *Aliment Pharmacol Ther*. 2013;38(5):460-466; Hashash JG et al. *Gastroenterol Hepatol* (N Y). 2015;11(2):96-102.

Effect of IBD on Pregnancy

- Disease activity is the strongest predictor of adverse pregnancy outcomes

- Active disease at conception: Increased risk of
  - Fetal loss
  - Preterm birth
- Flare during pregnancy: Increased risk of
  - Low birth weight, small for gestational age, intrauterine growth restriction
  - Preterm birth
  - Eclampsia

Nielsen OH et al. *Scand J Gastroenterol*. 1984;19(6):724-732; Reddy D et al. *Am J Gastroenterol.* 2008;103(5):1203-1209; Leung KK et al. *Inflamm Bowel Dis*. 2021;27(4):550-562.

Preconception Planning and Counseling

- Timing of pregnancy
  - Steroid-free remission x 3-6 months prior to conception
  - Stable dose of steroid-sparing therapy
- Confirm remission (now / in recent past)
  - CRP / fecal calprotectin / colonoscopy / MRE
- Assess current therapies
  - Stop methotrexate x 3-6 months prior to conception (abortifacient, teratogenic)
  - Small molecule therapy (JAKi, S1PR modulator): Limited data, assess risk and benefits
  - If need to stop / change therapy / optimize therapy
    - Reassess after 3 months and ensure disease is in remission

CRP = C-reactive protein; MRE = magnetic resonance enterography; JAKi = Janus kinase inhibitor; S1PR = sphingosine 1 phosphate receptor.
Mahadevan U et al. *Gastroenterology*. 2019;156(5):1508-1524.

Preconception Planning and Counseling

- Optimize patient's health
  - Correct deficiencies (Fe, B12);
    - Folic acid 2 mg/day if on sulfasalazine, if SB resection/ SB disease
  - Up to date on vaccinations and cancer screening (pap smear, skin, colon)
  - Assess for malnutrition
  - D/c smoking, alcohol, opioids

- Coordinate care
  - GI/IBD, maternal fetal medicine (or ObGyn comfortable w/ IBD)
  - Reinforce importance of adherence to medications
  - Discuss disease, maternal and fetal monitoring

SB = small bowel; GI = gastrointestinal; ACOG = American College of Obstetricians and Gynecologists.
Conradt E et al. *Pediatrics*. 2019;144(3):e20190128; ACOG. *Obstet Gynecol*. 2019;133(1):e78-e89.

Congenital Anomalies in Infants Born to Mothers With IBD

- Large UK database – 1990-2010
- 1,703 IBD vs 384,811 control
- Equal rates: 2.7% vs 2.8%

	OR	CI 95%
Any congenital anomaly	0.98	0.73-1.31
5-ASA	0.82	0.42-1.61
Corticosteroids	0.48	0.15-1.50
Thiopurines	1.27	0.48-3.39

ASA = aminosalicylic acid; OR = odds ratio; CI = confidence interval.

Ban L et al. *Gastroenterology*. 2014;146(1):76-84.

Biologics in Pregnancy

- Active transport of IgG from the mother across the placenta
  - Starts in 2nd trimester, majority occurring in 3rd trimester
  - CZP lacks Fc portion → NO placental transfer (CRIB study)
  - Drug level infant blood > mother
  - Persists longer in the newborn than the mother (up to 9-12 months)

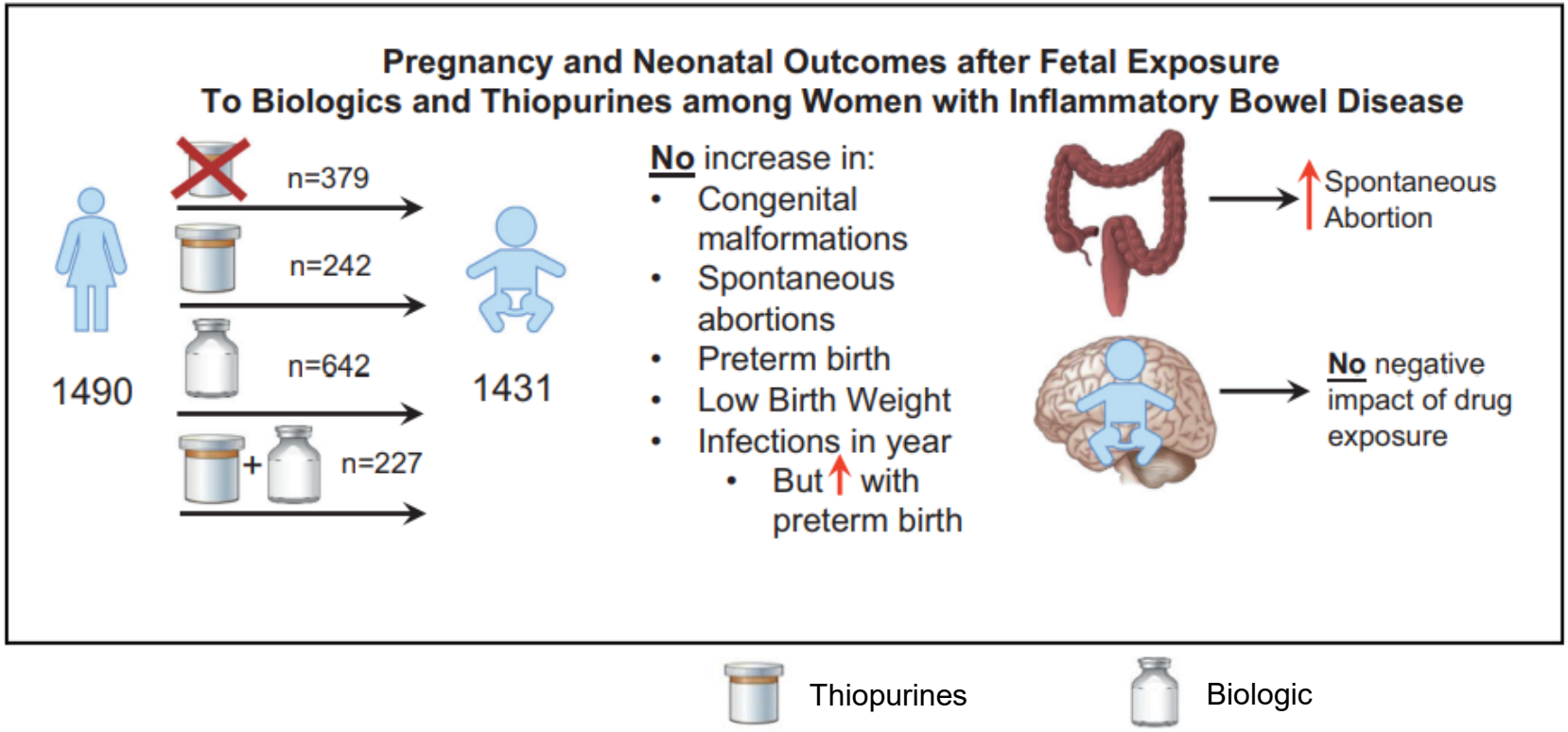
- EVASION French database: 8,726 women with IBD / 1,457 on anti-TNF
  - Increased risk of flare if TNFi stopped > week 24
  - No increased risk of infections in infants whether TNFi stopped or continued

Continue biologic during the entire pregnancy

Ig = immunoglobulin; CZP = certolizumab pegol; FC = fecal calprotectin; TNF = tumor necrosis factor.

Julsgaard M et al. *Gastroenterology*. 2016;151(1):110-119; Mahadevan U et al. *Clin Gastroenterol Hepatol*. 2013;11(3):286-292; Luu M et al. *Am J Gastoenterol*. 2018;113(11):1669-1677; Moens A et al. *Aliment Pharmacol Ther*. 2020;51(1):129-138.

PIANO: Pregnancy Outcomes by Biologic and/or Thiopurines Exposure

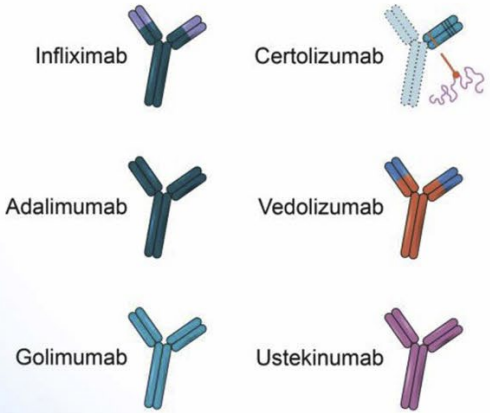


Mahadevan U et al. *Gastroenterology*. 2021;160(4):1131-1139.

Pregnancy Outcomes in Mothers With IBD on Biologics vs Non-IBD Mothers

Study group

Women on biologics:

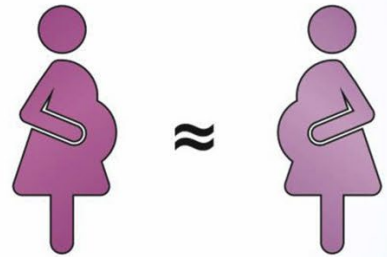


Studies included

Outcome	Studies	Participants	Pooled prevalence	
			Biologics	General population
Early pregnancy loss	37	4410	8 %	14 %
Preterm birth	32	3466	9 %	11 %
Stillbirth	25	4143	0 %	2 %
Low birth weight	23	1943	8 %	6 %
Congenital malformation	44	5176	1 %	3 %

Findings

Adverse pregnancy outcomes:



IBD women on biologics (including 3rd trimester)

General population

Systemic review and meta-analysis of 48 studies, including 6,963 patients on biologics

Mahadevan U et al. *Gastroenterology*. 2021;160(4):1131-1139.

Biologics in Pregnancy

- Resume biologic after delivery (if no infection, and wound healing)
  - 24 hours after vaginal delivery
  - 48 hours after C-section

- No live virus vaccine for the infant in the first 9 months (except CZP)
  - Rotavirus
  - BCG

- MMR/varicella can be given to breastfeeding mothers at 1 year

BCG = Bacille Calmette-Guérin; MMR = measles, mumps, rubella.

Mahadevan U et al. *Gastroenterology*. 2019;156(5):1508-1524.

Small Molecule Drugs and IBD

- Small molecules
  - JAKi: Tofacitinib, upadacitinib
  - S1PR agonist: Ozanimod
- Cross the placenta in 1st trimester, during organogenesis
  - Fetal malformations in animal studies
  - Limited data in humans to make conclusions on their safety during pregnancy

- Recommendations: Effective birth control During therapy and
  - Tofa: For 1 week after last dose
  - Upa: For 4 weeks after last dose
  - Oza: For 3 months after last dose

Mahadevan U et al. *Inflamm Bowel Dis*. 2018;24(12):2494-2500.

Delivery in Patients With IBD

- IBD is NOT an indication for C-section
  - Method of delivery should be determined by obstetrician

- Recommend C-section if
  - IPAA
  - Active perianal Crohn's disease
  - H/o rectovaginal fistula

  - Risk of 4th-degree laceration, anal sphincter dysfunction, worsening/recurrence of fistula w/ vaginal delivery

IPAA = ileal pouch-anal anastomosis.

Kitayama T et al. *Surg Today*. 2005;35(3):211-215; Ravid A et al. *Dis Colon Rectum*. 2002;45(10):1283-1288; Beniada A et al. *J Gynecol Obstet Biol Reprod* (Paris). 2005;34(6):581-588.

IBD and Breastfeeding

- Most studies report a significant protective effect of breastfeeding against IBD risk, when breastfeeding >12 months

- Breastmilk from mothers with IBD vs healthy mothers
  - Increased levels of pro-inflammatory cytokines
  - Lower levels of immunoprotective components of breastmilk such as IgA, sugar metabolite (lactose), and 2-aminobutyrate
  - Impact on the infant gut microbiome? Risk of IBD in offspring?

Agrawal M et al. *EClinicalMedicine*. 2021;36:100884; Meng X et al. *J Crohn's Colitis*. 2019;13(4):431-441.

IBD Medications and Breastfeeding

- 5-ASA – Safe
  - Sulfasalazine: Sulfapyridine metabolites → hemolysis if infant G6PD deficiency
- Steroids: Subtherapeutic levels in breast milk – Safe
- Thiopurines and biologics: <1% to undetectable levels in breastmilk – Safe
  - No difference in the rate of infection at 1 year (exposed vs unexposed)
  - No difference in achieving developmental milestones at 1 year (exposed vs unexposed)
  - No “pump and dump” after SQ/IV dose

- Avoid breastfeeding on
  - MTX (active metabolite in breastmilk)
  - Small molecule therapies (not enough data)

MTX = methotrexate.

Drugs and Lactation Database. 2006-2021; Matro R et al. *Gastroenterology*. 2018;155(3):696-704.

IBD Flare During Pregnancy

- Normal lab variations during pregnancy
  - Elevated CRP, ESR (monitor overall trend or use FCP instead)
  - Elevated AlkPhos
  - Decreased Hb and albumin

- Fecal calprotectin
- Stool studies, r/o *C. difficile* ++
- Imaging: MRI, w/o gadolinium in 1st trimester (teratogenic); Intestinal Ultrasound
- Flex sig, Safe any semester
  - Unsedated, minimal prep w/ enema
  - ASGE: Left lateral tilt position (to avoid decreased maternal and placental perfusion)
  - Colonoscopy w/ sedation needs fetal monitoring

ESR = erythrocyte sedimentation rate; Hb = hemoglobin; ASGE = American Society for Gastrointestinal Endoscopy.

De Lima A et al. *J Crohn's Colitis*. 2015;9(7):519-524; Julsgaard M et al. *Inflamm Bowel Dis*. 2017;23(7):1240-1246; ASGE Standard of Practice Committee. *Gastrointest Endosc*. 2012;76(1):18-24.

IBD Flare During Pregnancy

- Do not initiate AZA/6MP
  - Risk of neutropenia and pancreatitis
  - Slow onset of action
- Antibiotic: Amoxicillin-clavulanic acid
  - Avoid cipro (musculoskeletal)
  - Avoid metronidazole (1st trimester)
- Steroids
  - Lowest dose, shortest duration
  - Prednisolone (1/8th-1/10th cross placenta)
  - Budesonide if appropriate

AZA = azathioprine; 6MP = 6-mercaptopurine.

Pregnancy Outcomes With Steroids Exposure

- PIANO: 1,490 mothers with IBD / 1,431 live births recorded
- 432 (30%) steroid exposure at preconception or during pregnancy

- CS use associated with
  - Preterm birth
  - Small for gestational age, intrauterine growth restriction, low birth weight
  - NICU admission
  - 2nd/3rd trimester corticosteroid use: Serious infections requiring hospitalization in infants at 9 and 12 months
  - Gestational DM
- No increased risk of
  - Orofacial clefts and other congenital malformations
  - Developmental delay

CS = corticosteroids; NICU = neonatal intensive care unit; DM = diabetes mellitus.

Odufalu FD et al. *Gut*. 2022; 71(9):1766-1772

IBD Flare During Pregnancy

- Mesalamine: Initiate any time during pregnancy in mild UC
- Biologic
  - Induction and maintenance
  - Modify dose/frequency for patients already on biologic
- Cyclosporine A as rescue therapy in steroid-refractory UC
- Hospitalized: DVT prophylaxis
- Surgery: Preferably in 2nd trimester

Control the flare quickly and effectively to minimize negative pregnancy outcomes

DVT = deep vein thrombosis.

Reddy D et al. *Am J Gastroenterol.* 2008;103(5):1203-1209.

Summary: IBD and Pregnancy

- Fertility: Similar to general population
  - Discuss effect of IPAA on fertility in young patients
- Most important factors for good pregnancy outcome
  - Preconception counseling
    - Review family planning goals with all patients of child-bearing age (both men + women)
  - Stable steroid-free remission at time of conception x 3-6 months
  - Maintaining remission during pregnancy with adequate therapies
    - 5-ASA, thiopurines, biologics safe during pregnancy and breastfeeding
- Delivery C-section if perianal Crohn's, IPAA, h/o RV fistula
- Treat flare in pregnancy appropriately

RV = rectovaginal.

Resources

Clinicians

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AGA SECTION

Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway: A Report From the American Gastroenterological Association IBD Parenthood Project Working Group

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Patients with IBD

ibd PARENTHOOD PROJECT

Mahadevan U et al. *Gastroenterology*. 2019;156(5):1508-1524.