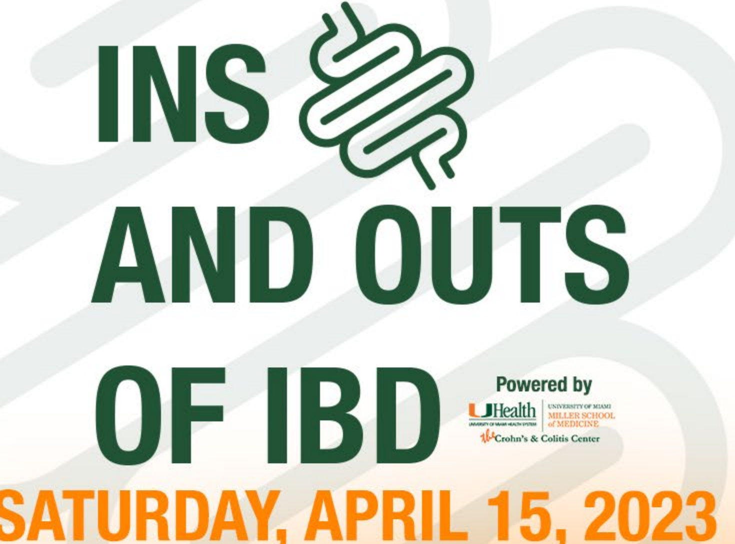
INS AND OUTS OF IBD



SATURDAY, APRIL 15, 2023

SUPPORTED BY EDUCATIONAL GRANTS FROM JANSSEN BIOTECH, INC., PFIZER INC., AND TAKEDA PHARMACEUTICALS, U.S.A, INC.

Pregnancy and Fertility in IBD

Siobhan Proksell, MD
Assistant Clinical Professor
University of Miami Miller School of Medicine

Disclosures

Siobhan Proksell, MD

- **Research Support:** Pfizer

IBD + Pregnancy: The Numbers

- 1.3% of the US population (3 million people!)
  - ½ female
    - *Most* carry this diagnosis during childbearing years
- Fertility
  - CD/UC in remission: same as general population
  - S/p IPAA, proctectomy, or ostomy: ↓
  - Active disease: ↓
- REI indications: age, timing

IBD + Pregnancy: The Patient Perspective

- Voluntary childlessness rates: 17% vs 6%
- Recent study evaluating perspective of minority women
  - Although most (70%) noted importance of compliance during pregnancy, they also believed there would be a negative fetal impact
- Discussion with physician inversely related to rates of voluntary childlessness

IBD + Pregnancy: The Preparation

Discuss *before* pregnancy

- Medications
- Remission
- Pre-conception, pregnancy, delivery and post-delivery
- Infant considerations

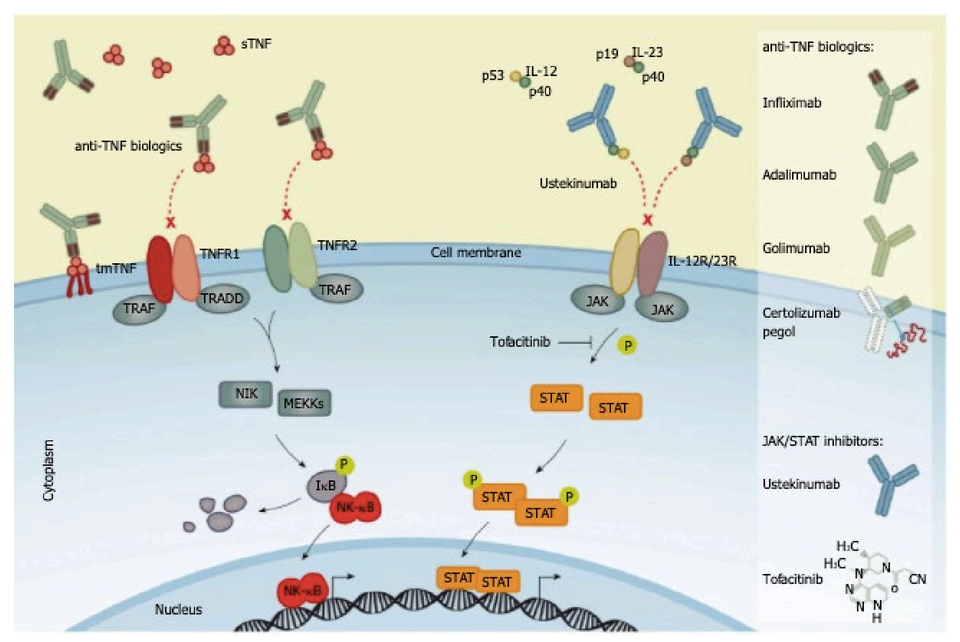
- IBD Parenthood Project
- IBD in Pregnancy Clinical Care Pathway (AGA)

IBD + Pregnancy: Care Team

- Gastroenterologist
- Obstetrician
  - MFM or regular OB
- CRS, if needed
- Other considerations:
  - Nutrition, lactation, behavioral health

IBD + Pregnancy: The Medications

- Steroids
- Immunomodulators
  - MTX, azathioprine, 6MP
- Biologics
  - Anti-TNF, anti-integrin, anti-IL-12/IL-23
- Small molecules
  - JAK inhibitors, S1P receptor modulators



IBD + Pregnancy: Medication Basics

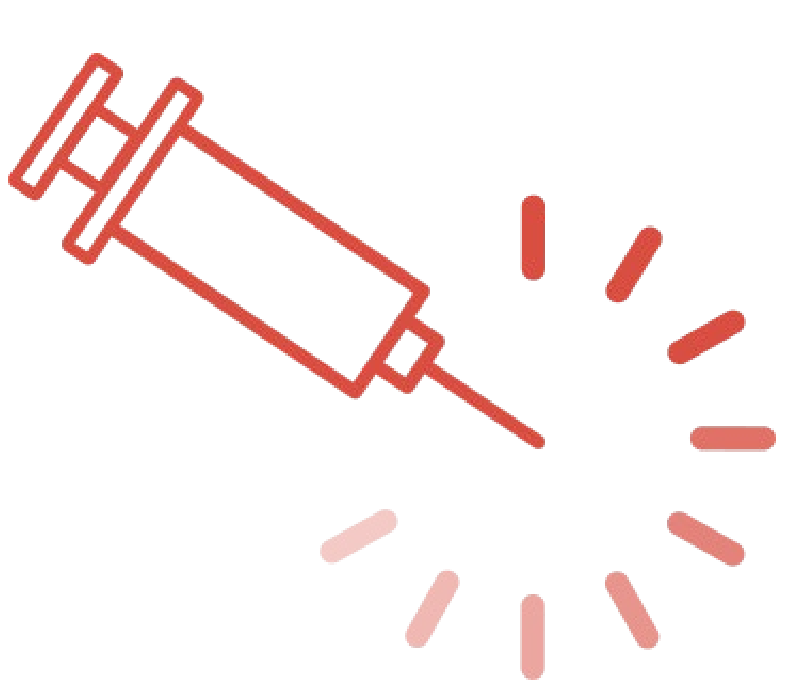
- Discontinue MTX *prior* to conception
  - At least 3 months
- Avoid steroids if possible
  - 1st trimester, ↑ cleft palate risk

IBD + Pregnancy: Mediations to Continue

- Mesalamines*
  - All phthalate free except Azulfadine EN
  - SFZ concerns
- Thiopurines*
  - Continue if monotherapy
  - Consider stopping if combination therapy
  - Don’t start during pregnancy

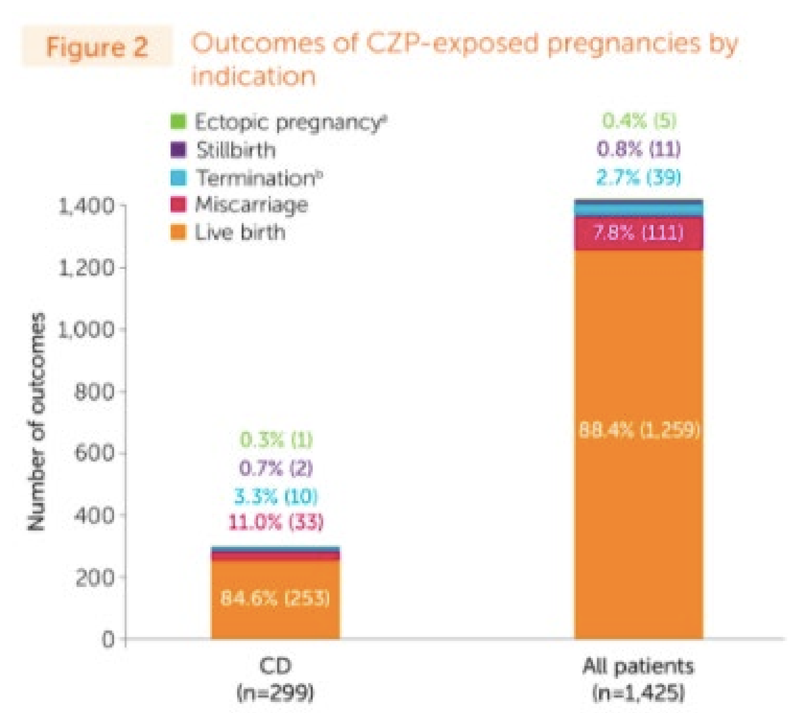
IBD + Pregnancy: The [Classic] Medications

- Infliximab
- Adalimumab
- Certolizumab
  - Pegylated
  - Does not cross placenta
- Golimumab



IBD + Pregnancy: The [Classic] Medications

	IFX gestational	IFX pre-gestational	Non-biologic
# pregnancies	106	66	106
Known outcome, n (%)	99 (93.4)	63 (95.5)	90 (84.9)
Live birth, n (%)	81 (81.8)	57 (90.5)	82 (91.1)
Spontaneous abortion, n (%)	16 (16.2)	4 (6.3)	8 (8.9)
Elective abortion, n(%)	2 (2.0)	2 (3.2)	0
Healthy infant, n (%)	75 (92.6)	52 (91.2)	72 (87.8)
Congenital abnormality, n (%)	1 (1.2)	1 (1.8	3 (3.7)
Neonatal problem, n (%)	5 (6.2)	4 (7.0)	7 (8.5)
Prolonged hospitalization, n (%)	5 (4.7)	5 (7.6)	12 (11.3)



IBD + Pregnancy: The [Classic] Medications

Timing of administration

- Adjust timing of dose in attempt to deliver at trough
- Resume after delivery
  - 24 hours after vaginal
  - 48 hours after c-section

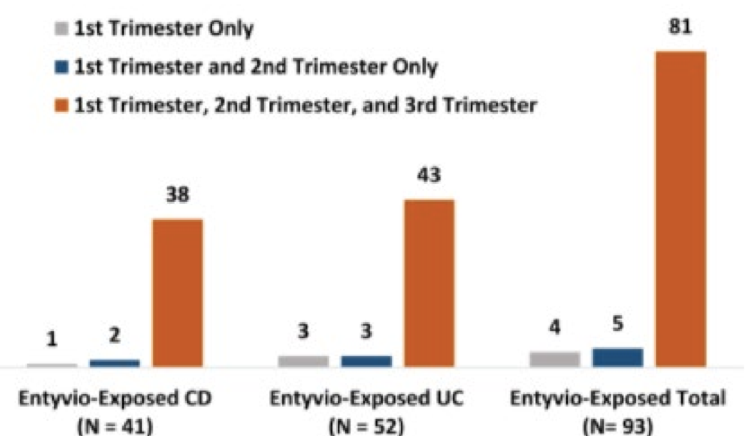
Adjustments prior to estimated delivery date

- Infliximab
  - 6-10 weeks prior (4-6 weeks if Q4week dosing)
- Adalimumab
  - 2-3 weeks prior (1-2 weeks if weekly dosing)
- Golimumab
  - 4-6 weeks prior
- *Certolizumab: continue regular dosing

IBD + Pregnancy: The [Newer] Medications

Anti-integrin: vedolizumab

- Vedolizumab Pregnancy Exposure Registry



	Vedolizumab exposed (N = 93)	Disease matched (N = 104)	Healthy controls (N = 98)
Live born infant n/N (%)	88/93 (94.6)	99/104 (95.2)	85/98 (86.7)
Spontaneous abortion n/N (%)	3 (9.4)	3 (6.1)	1 (5.7)
Termination; n/N (%)	0/93 (0)	0/104 (0)	0/98 (0)
Still birth; n/N (%)	0/93 (0)	1/104 (1.0)	0/98 (0)
Preterm rate	13 (15.3)	6 (6.1)	6 (7.3)
Mean birthweight (g)	3405.4	3427.9	3307.4
Major birth defects; n/N (%)	5/91 (5.5)	7/103 (6.8)	4/86 (4.7)
Serious infections ($\leq$1 y/o); n/N (%)	3/92 (3.3)	1/99 (1.0)	1/88 (1.1)
Screening with concern (up to 1 y/o); n/N (%)	9/48 (18.8)	19/85 (22.4)	8/56 (14.3)

IBD + Pregnancy: The [Newer] Medications

Anti-IL-12/IL-23: Ustekinumab

- Literature demonstrates similar birth outcomes as compared to the general population

Safety data through 2019

	Live Birth	Elective/ Induced Abortion	Spontaneous Abortion	Live Birth with Congenital AEs
All Cases	68.8%	9.0%	18.4%	2.7%
Prospective Cases	75.7%	7.8%	13.5%	2.7%
Retrospective Cases	57.7%	11.0%	26.4%	2.7%
General Population	62.9%	19.4%	17.9%	4.0%

IBD + Pregnancy: The [Newer] Medications

JAK inhibitor: Tofacitinib

- Other agents preferred
  - At least avoid during 1st trimester
- Animal studies show in utero fetal harm
- Limited data
  - 11/1157 pregnancies with maternal exposure
- Pregnancy registry

	Maternal Exposure (11/1157) No. (%)	Paternal Exposure (14/1157) No. (%)
Healthy newborn	4 (36.4)	11 (78.6)
Medical termination	2 (18.2)	0 (0.0)
Neonatal death	0 (0.0)	0 (0.0)
Fetal death	0 (0.0)	0 (0.0)
Congenital malformations	0 (0.0)	0 (0.0)
Spontaneous abortion	2 (18.2)	0 (0.0)
Pending or lost to follow up	3 (27.3)	3 (21.4)

IBD + Pregnancy: The [Newer] Medications

S1P receptor modulator: Ozanimod

- Other agents preferred
- Animal studies have shown in-utero exposure may cause fetal harm
- Data from MS trial
  - 42 pregnancies/1868 females
- Elimination takes approximately 3 months

	Ozanimod exposed pregnancies (N = 42)
Live born infant n/N (%)	27/42 (64.3)
Spontaneous abortion n/N (%)	6/42*+(14.3)
Termination n/N (%)	9/42 (21.4)
Preterm rate n/N (%)	3/27 (11.1)

Outcome, n	UC	CD
Pregnancies	**9**	**3**
Healthy live birth	2	1
Congenital abnormality	0	0
Premature	0	0
Ongoing	2	2
Spontaneous early loss	2	0
Elective termination	3	0

*loss of one twin.
+ Rate of spontaneous abortion in general population 12-22%.

IBD + Pregnancy: The [Future] Medications

JAK1 inhibitor: Upadacitinib

- Other agents preferred
- Animal studies have shown in utero exposure can cause fetal harm
- No effect on fertility

JAK1 inhibitor: Filgotinib

- Other agents preferred
- Decreased fertility + impaired spermatogenesis in animal studies
- Animal studies have shown in utero exposure can cause fetal harm

What About Males?

- **Paternal exposure** to immunosuppressive or biologic therapies near or at the time of conception **did not** lead to increased risk of adverse neonatal outcomes
- **No increased risk of**
  - Major congenital malformations
  - Low birth weight
  - Preterm birth

Infant Care

- Breast feeding
  - Medications safe, in general
    - PIANO – no increased risk of infection in first 12 months of life
    - SFZ least preferred Asa (higher excretion of metabolite, unk effect)
    - MTX – not enough info
    - Small molecules – generally recommended against
- Vaccinations in biologics*
  - NO LIVE VACCINES IN FIRST 6 MONTHS OF LIFE
  - Okay to give thereafter, and if ongoing breast feeding

Additional Considerations

- Will new medications affect future fertility?
- In whom should we consider fertility preservation, if anyone?

Take Home Points

- Knowledge is essential
- Remission is key
  - Best chance of a healthy pregnancy
- Fertility affected by surgery, active disease
- Be aware of therapy implications

- Women with IBD can have healthy pregnancies!

References

1. Mahadevan U, Robinson C, et al. Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway: A report from the AGA IBD Parenthood Project Working Group. *Gastro*. 2019;156(5):1508-24.
2. Jain R, et al. Knowledge and attitudes toward fertility among minority women with inflammatory bowel disease. P0555. Abstract presented at ACG October 24, 2021.
3. Mills BS, et al. Preceptions of pregnancy and lactation from the pregnancy and lactation autoimmune network registry. *J Rheumatol.* 2020;47(1):149-54.
4. Pederson J, et al. Inflammatory pathways of importance for management of inflammatory bowel disease. *World J of Gastroenterol.* 2014;20(1):64-77.
5. Dubinsky M, et al. Pharmacovigilance Data on Pregnancy Outcomes in Women With Crohn's Disease Exposed to Certolizumab Pegol. Abstract presented at ACG; October 24, 2021.
6. Chambers CD, et al. Birth outcomes in women who have taken adalimumab in pregnancy: A prospective cohort study. *PLosONE.* 2019;14(10):e0223603.
7. Lichtenstein GR, et al. Pregnancy outcomes reported during the 13 years TREAT registry: A descriptive report. *Am J Gastroenterol.* 2018;113(11):1678-88.
8. Tikhonov I, Volger S, Lin CB, et al. Pregnancy outcomes in women with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis treated with ustekinumab. Poster presented at: American Academy of Dermatology; June 12-14, 2020.
9. Abraham B, Ott E, Busse C, et al. Pregnancy outcomes in women exposed to ustekinumab in the Crohn's disease and ulcerative colitis clinical trials. Abstract presented at: Digestive Disease Week; May 21-23, 2021.
10. Gorodensky JH, Bernatsky S, Afif W, et al. Risk of serious infections in offspring exposed in utero to ustekinumab or vedolizumab. Abstract presented at: Digestive Disease Week May 21-23, 2021.
11. Chambers CD, et al. The vedolizumab pregnancy exposure registry: an OTIS pregnancy study update. Abstract presented at: ACG October 25, 2021.
12. Gorodensky JH, Bernatsky S, Afif W, et al. Risk of serious infections in offspring exposed in utero to ustekinumab or vedolizumab. Abstract presented at: Digestive Disease Week May 21-23, 2021.
13. Mahadevan U, Dubinsky MC, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis*. 2018 Dec;24(12)2494-2500.
14. Pfizer medical information: Xeljanz/Xeljanz XR use in specific populations. https://www.pfizermedicalinformation.com/en-us/xeljanz/population-use#data. Accessed Nov 4, 2021.
15. Minton N, Henry A, et al. Pregnancy outcomes in the ozanimod multiple sclerosis clinical development program. *Neurology*. 2021;96(15).
16. Dubinsky, et al. DOP53 Pregnancy outcomes in the ozanimod clinical development program in relapsing multiple sclerosis, Ulcerative Colitis, and Crohn's Disease. *J Crohn's ad Colitis*. 2021; 15(1):S088-89.
17. Napolitano M, Ruggerio A, et al. New emergent therapies for atopic dermatitis: A review of the safety profile with respect to female fertility, pregnancy, and breastfeeding. *Dermatologic Therapy*. 2021;32:e14475.
18. Upadacitinib FDA prescribing information, pregnancy section 8.1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211675s000lbl.pdf Accessed Nov 4, 2021.
19. Filgotinib animal model data, section 5.3. https://www.ema.europa.eu/en/documents/product-information/jyseleca-epar-product-information_en.pdf Accessed Nov 4, 2021.
20. Meserve J, Luo J, et al. Paternal Exposure to Immunosuppressive and/or Biologic Agents and Birth Outcomes in Patients With Immune-Mediated Inflammatory Diseases. *Gastroenterology.* 2021;161:107–115.