Current Clinical Landscape

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Pregnancy in IBD And Neonatal Outcomes

Disclosures

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Speakers Bureau/Honoraria: None	**Other:** DSMB: Merck/Prometheus Biosciences

Tax for Reproductive Potential

- **1977**: FDA policy recommended excluding women of childbearing potential from Phase I/Phase II drug trials
  - Even if on contraception, single, or vasectomized husbands
- **1986**, NIH policy that encouraged researchers to include women
  - Policy had been poorly communicated and inconsistently applied
- **1993** NIH Revitalization Act (Public Law 103-43): Women and Minorities as Subjects in Clinical Research (Dr. Healy, NIH Director)
  - Monitor recruitment of women and minorities
- **1998** Final rule on the content and formation of a New Drug Application (21 CFR §314.50 (d)(5))
  - Requires that effectiveness and safety data be presented for demographic subgroups including gender
- **2022** draft Guidance to Industry: *Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials*
  - Agency describes broadening clinical trial eligibility and increasing diversity of trial participants including additional demographics such as pregnancy status and lactation status
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations

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Accessed 2/10/2022 https://orwh.od.nih.gov/toolkit/recruitment/history#7

But we are along way past that right?

- Women who become pregnant must drop out of a study, even if drug class has known safety or low risk (anti-TNF, IL-23s)
- Exclusion of women of child bearing age from receiving jakinibs
- Medications with well-established safety (anti-TNFs) discontinued in pregnancy
  - 68% of women who stopped anti-TNF on the advice of their Rheumatologist[1]

1. Talabi, ACR Open Rheumatology, 3: 475-483. https://doi.org/10.1002/acr2.11240

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Importance of Treating IMIDs in Pregnancy

IBD: Disease Activity & Adverse Events

- Disease Activity increases rate of adverse events

- Overall increased risk of:
  - Spontaneous Abortion
  - Preterm Birth
  - Low Birth Weight/Small for Gestational Age
  - Hypertensive Disorders of Pregnancy, Pre-eclampsia
  - Post-partum Hemorrhage
  - Caesarean section

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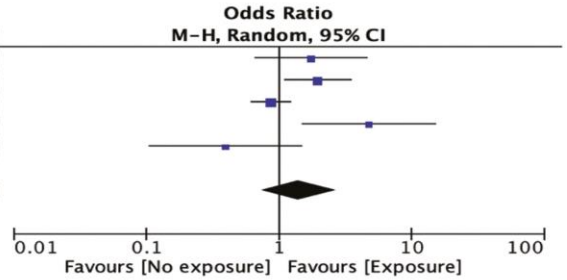
Brondfield and Mahadevan
Nat Rev Gastroenterol Hepatol (2023)

Stopping Biologics is Associated with Disease Flare: Systematic Review and Metanalysis

A

Study or Subgroup	Biologic exposure Events	Total	No biologic exposure Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bennett 2019	24	73	7	32	18.2%	1.75 [0.66, 4.61]
Lichtenstein 2018	58	95	44	99	24.7%	1.96 [1.11, 3.47]
Mahadevan 2020	62	642	93	849	28.2%	0.87 [0.62, 1.22]
Rekawek	8	70	5	190	15.5%	4.77 [1.51, 15.13]
Yu 2020	3	34	14	71	13.5%	0.39 [0.11, 1.48]
Total (95% CI)		**914**		**1241**	**100.0%**	**1.41 [0.74, 2.70]**
Total events	155		163			

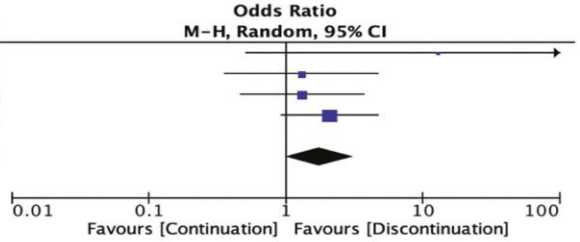
Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 15.05$, df = 4 (P = 0.005); $I^2 = 73\%$
Test for overall effect: Z = 1.04 (P = 0.30)



B

Study or Subgroup	Biologic held before T3 Events	Total	Biologic continued Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Arguelles-Arias 2012	3	3	3	9	3.0%	13.00 [0.51, 330.48]
de Lima 2015	8	51	4	32	19.0%	1.30 [0.36, 4.74]
Seirafi 2014	27	85	6	23	29.5%	1.32 [0.47, 3.72]
Yu 2020	13	28	52	178	48.4%	2.10 [0.93, 4.72]
Total (95% CI)		**167**		**242**	**100.0%**	**1.77 [1.01, 3.10]**
Total events	51		65			

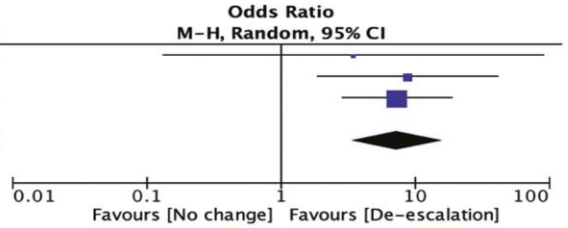
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.16$, df = 3 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 1.98 (P = 0.05)



C

Study or Subgroup	Therapy de-escalated Events	Total	Therapy continued Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Arguelles-Arias 2012	2	2	6	10	5.7%	3.46 [0.13, 90.68]
Julsgaard 2014	5	10	5	49	25.2%	8.80 [1.87, 41.32]
Yu 2020	18	25	47	181	69.1%	7.33 [2.88, 18.66]
Total (95% CI)		**37**		**240**	**100.0%**	**7.36 [3.38, 16.00]**
Total events	25		58			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.26$, df = 2 (P = 0.88); $I^2 = 0\%$
Test for overall effect: Z = 5.04 (P < 0.00001)



Inflamm Bowel Dis, Volume 28, Issue 7, July 2022, Pages 1090–1099, https://doi.org/10.1093/ibd/izab206

Rheumatoid Arthritis

- Retrospective cohort study using Healthcare Cost and Utilization Project - National Inpatient Sample (HCUP-NIS) from the USA.
  - All births that took place from 2004 to 2013 identified, classified as having RA or not
  - 8,417,607 births in cohort, 6068 were RA
- Women with RA were *more likely* to develop
  - pre-eclampsia/eclampsia
  - gestational diabetes
  - preterm premature rupture of membranes
  - placental abruption and placenta previa
  - caesarean section.
- Postpartum
  - wound complications
  - thromboembolisms
- Neonates:
  - Congenital anomalies
  - Small for gestational age
  - Preterm birth

Aljary The Journal of Maternal-Fetal & Neonatal Medicine Volume 33, 2020 - Issue 4

ACR Recommendation

- We *conditionally* recommend continuing tumor necrosis factor inhibitor therapy with infliximab, etanercept, adalimumab, or golimumab prior to and during pregnancy. The tumor necrosis factor inhibitor certolizumab does not contain an Fc chain and thus has minimal placental transfer. We *strongly* recommend continuation of certolizumab therapy prior to and during pregnancy.
  - The Voting Panel agreed that if the patient's disease is under good control, these medications may be discontinued in the third trimester

Sammaritano Arthritis & Rheumatology Vol. 72, No. 4, April 2020, pp 529–556

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Disease Activity ↑ Adverse Outcomes

- Prospective rheum registries Sweden (SRQ) & Denmark (DANBIO)
- 1739 RA vs. 17390 control pregnancies
  - Disease Activity: DAS28, CRP, HAQ score
  - Treatment 9 mos before/during pregnancy
  - Adjusted for maternal characteristics, stratified by disease activity, medication use
- Increased aOR **PTB** 1.92 (1.56-2.35), **SGA** 1.93 (1.45-2.57)
  - With corticosteroids: PTB 2.11 (0.94-4.74)
  - With Biologics PTB 1.38 (0.66-2.89)
- Increased risk of C-section

Hellgren *Rheumatology*, Volume 61, Issue 9, September 2022, Pages 3711–3722

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Medications should be continued in preconception and pregnancy to avoid flares and reduce Adverse Outcomes

- The significant increase in pregnancy and neonatal complications in RA/IBD pregnancies is closely linked to disease activity and inflammation.
- Stopping low risk and effective steroid sparing therapies leads to increased suffering for the mother, post partum flares and WORSE outcomes for the baby
- **Healthy mother = Healthy baby**

Study Designs and Limitations

Limitations of Data

- Pregnant women are not included in clinical trials
- Unmeasured confounding is innate to uncontrolled studies
- Existing disease activity impacts decision to continue or discontinue therapy – the decision is not random
- Low event rates for adverse events
- Small cohort sizes

Types of Studies

1. Large Datasets (birds eye view)
    - Population based studies
        - Longitudinal assessment, parent-child linkage
        - Good assessment of diagnosis, pregnancy outcomes
        - Fair assessment of medication (prescription based)
        - Poor assessment of disease activity, lack of granular data
    - Insurance Claims Data
        - Lack of clinical data, fragmented care, absence of key data
2. Registries (PIANO) (more granular data)
    - Prospective Data Collection – extensive, granular
    - Limited by funding, objective markers of disease, finite
3. Pharmacovigilance data
    - limited by pt, provider reporting
4. Case Series
    - Small numbers, biased reporting

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Existing Data

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www.pianostudy.org

A national study of women with IBD and their children.

The PIANO research study looks at the safety of IBD medications in pregnancy and short- and long-term outcomes of the children.

PIANO: Pregnancy IBD And Neonatal Outcomes

- Patients were classified into four groups based on exposure to drugs taken between conception and delivery

Unexposed:	Group A:	Group B:	Group AB:
(can include steroids, ASA, antibiotics)	Azathioprine 6-mercaptopurine	Biologics (IFX, ADA, CZP,NAT)	Combination AZA/Biologic

- Exposure was defined as any use of AZA/6MP or a biologic agent at any time from 3 months prior to LMP to the end of the pregnancy
- Offspring of exposed women were compared to offspring of unexposed women with IBD during the same time period

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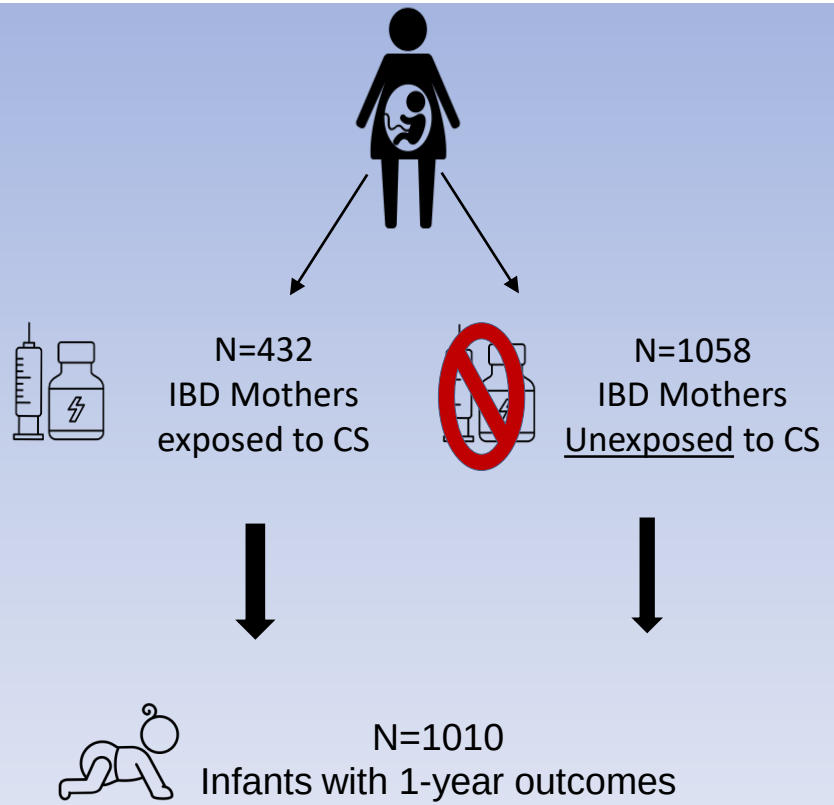
Methods

- Outcomes measured:
  - SAB, preterm birth, SGA, LBW, IUGR, C-section, NICU at birth
  - Placental disorders
  - Congenital malformations
  - Developmental Milestones
  - Infant Infections
    - Serious Infection → Requiring Hospitalization
    - Non-serious Infection → any reported infection without hospitalization
- Questionnaires were administered at study intake, each trimester, months 4,9,12 and annually thereafter until age 18.

Exposure to Corticosteroids in Pregnancy is Associated with Adverse Perinatal Outcomes Among Infants of Mothers with Inflammatory Bowel Disease: Results From The PIANO Registry



Maternal Outcomes with CS exposure

Adverse Outcomes of Pregnancy

- Pre-term birth, OR 1.8 (1.2-2.7)
- Low birth weight, OR 1.8 (1.1-2.9)
- NICU admission, OR 1.5 (1.0-2.3)

Infant Outcomes with CS exposure

No increased congenital malformations, OR 1.2 (0.8-1.9)

↑ Orofacial clefts T1

No increased risk of neurocognitive deficits in first 12 months of life

No increased risk of infection in first 12 months of life, OR 1.1 (0.9-1.4)

CS Corticosteroids; OR Odds Ratio; T1 First Trimester

Odufalu FD *Gut* 2021. doi: 10.1136/gutjnl-2021-325317

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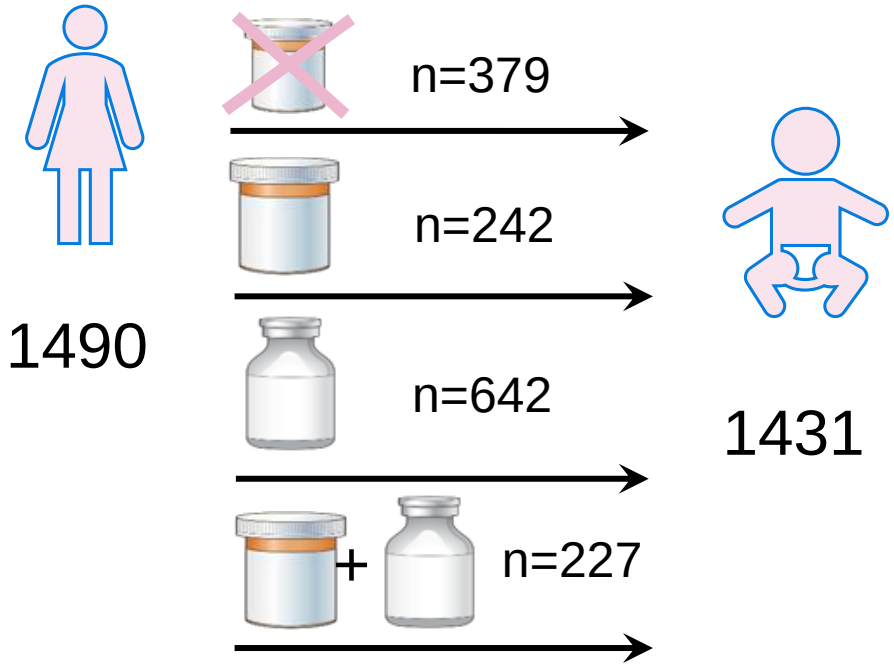
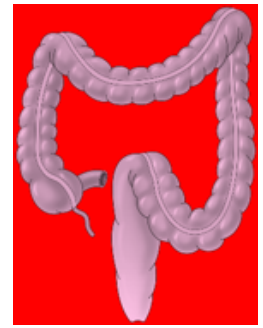
Gut

Pregnancy and Neonatal Outcomes After Fetal Exposure To Biologics and Thiopurines Among Women with Inflammatory Bowel Disease

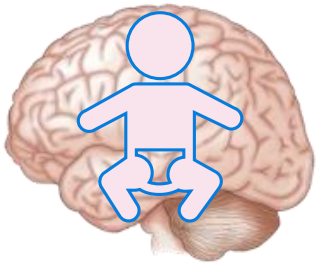


No increase in:

- Congenital malformations
- Spontaneous abortions
- Preterm birth
- Low Birth Weight
- Infections in year
  - But ↑ with preterm birth



↑ Spontaneous Abortion



No negative impact of drug exposure

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

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Placental Transfer

Variable	Infliximab	Adalimumab	Certolizumab pegol	Golimumab	Vedolizumab	Natalizumab	Ustekinumab
N=235	99	66	33	4	22	4	7
[Infant or Cord] [median µg/ml (range)] *	27.1 (0.1, 103.1)	9.1 (0.0, 26.0)	0.0 (0.0, 5.1)	3.4 (1.1, 4.1)	8.9 (3.0, 22.0)	1.8 (0.0, 3.9)	5.0 (0.6, 40.0)
[Maternal] [median µg/ml (range)]	12.0 (0.0, 129.3)	8.2 (0.0, 39.8)	25.0 (0.0, 56.4)	2.2 (0.5, 3.7)	13.0 (0.4, 44.0)	2.5 (0.0, 5.5)	4.0 (0.1, 18.9)
[Infant or Cord/Maternal] Ratio(median (range) **	2.4 (0.7, 8.0)	1.3 (0.4, 5.4)	0.0 (0.0, 0.1)	1.5 (0.0, 2.2)	0.5 (0.0, 1.7)	0.7 (0.7, 0.7)	1.4 (0.7, 13.7)
Days Since Last Maternal Dose[median (range)]	50.0 (6.0,133.0)	14.0 (1.0, 150.0)	13.0 (2.0, 30.0)	21.0 (18.0, 28.0)	29.0 (1.0, 84.0)	32.5 (6.0, 141.0)	35.0 (7.0, 74.0)
[Infant] at next Blood Draw^ [median µg/ml (range)]	0.6 (0.0, 7.0)	0.0 (0.0, 2.2)	0.0 (0.0, 0.0)	--	0.0 (0.0, 0.0)	--	0.1 (0.0, 0.2)

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

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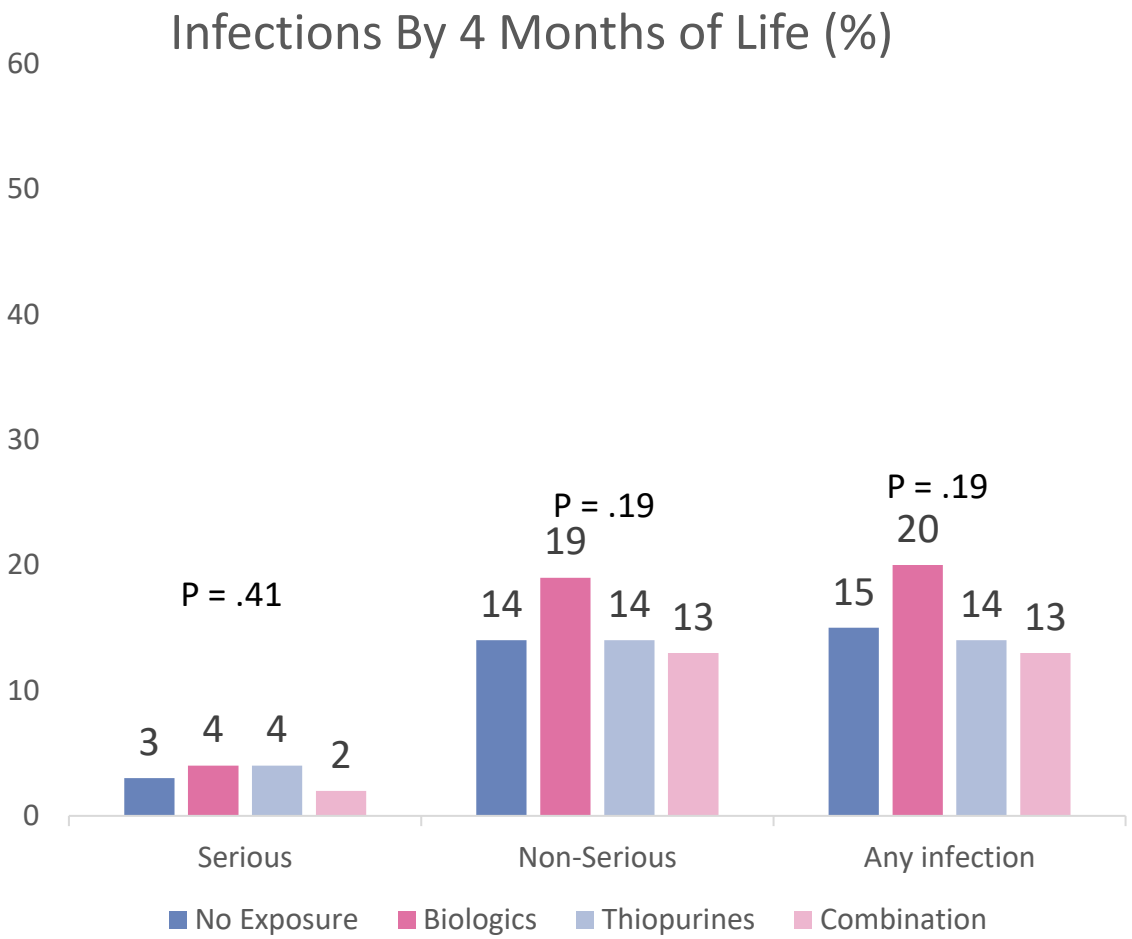
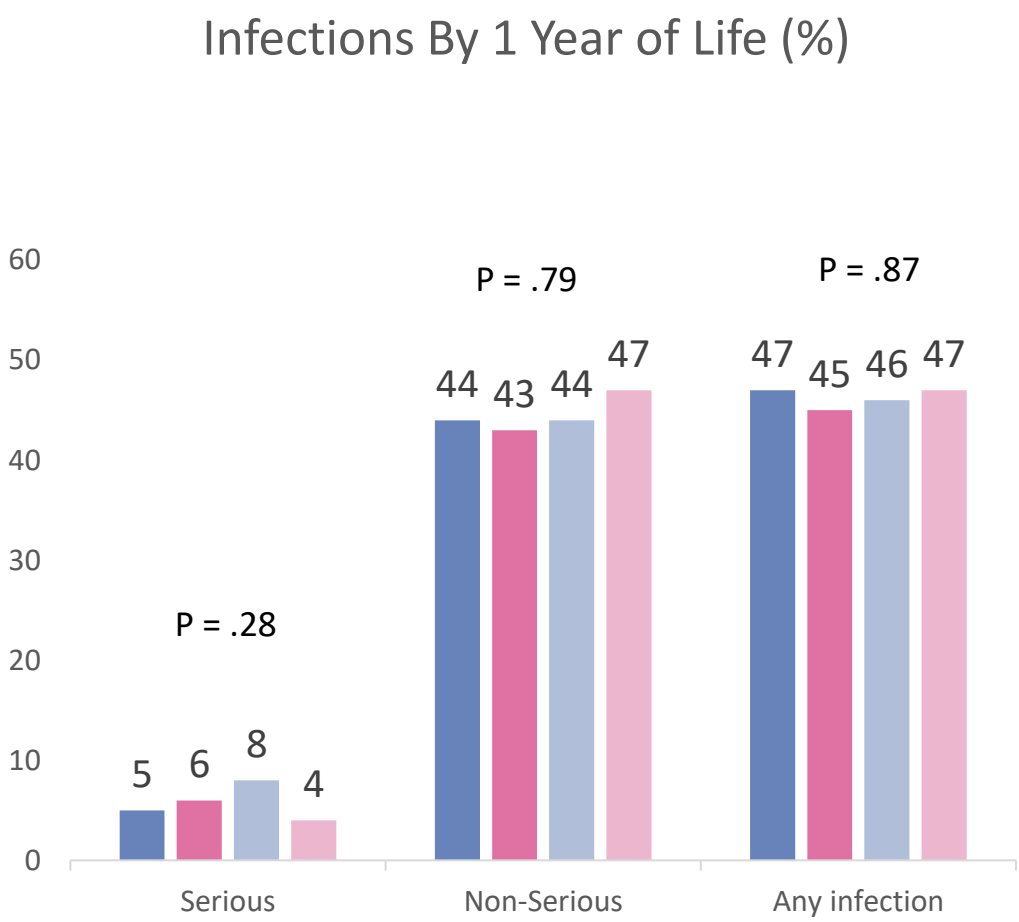
Infections After Fetal Exposure to Biologics and Thiopurines Among Women with IBD





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

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Biologics During Pregnancy in Women With Inflammatory Bowel Disease and Risk of Infantile Infections: A Systematic Review and Meta-Analysis

- Nine studies: 8,013 women with IBD → 8490 infants
  - 5,212 Crohn's disease, 2,801 ulcerative colitis
- NO increase in
  - Risk of **all** infantile infections (OR 0.91, 0.73-1.14)
  - Infantile antibiotic use (OR 0.91, 0.73-1.14)
  - Non-infection-related hospitalizations (OR 1.33, 0.95-1.86)
- Subgroup: ↑ infantile upper respiratory infections (OR 1.57, 1.02-2.40)

J. Gubatan et al. Am J Gastroenterol Oct 23, 2020 online

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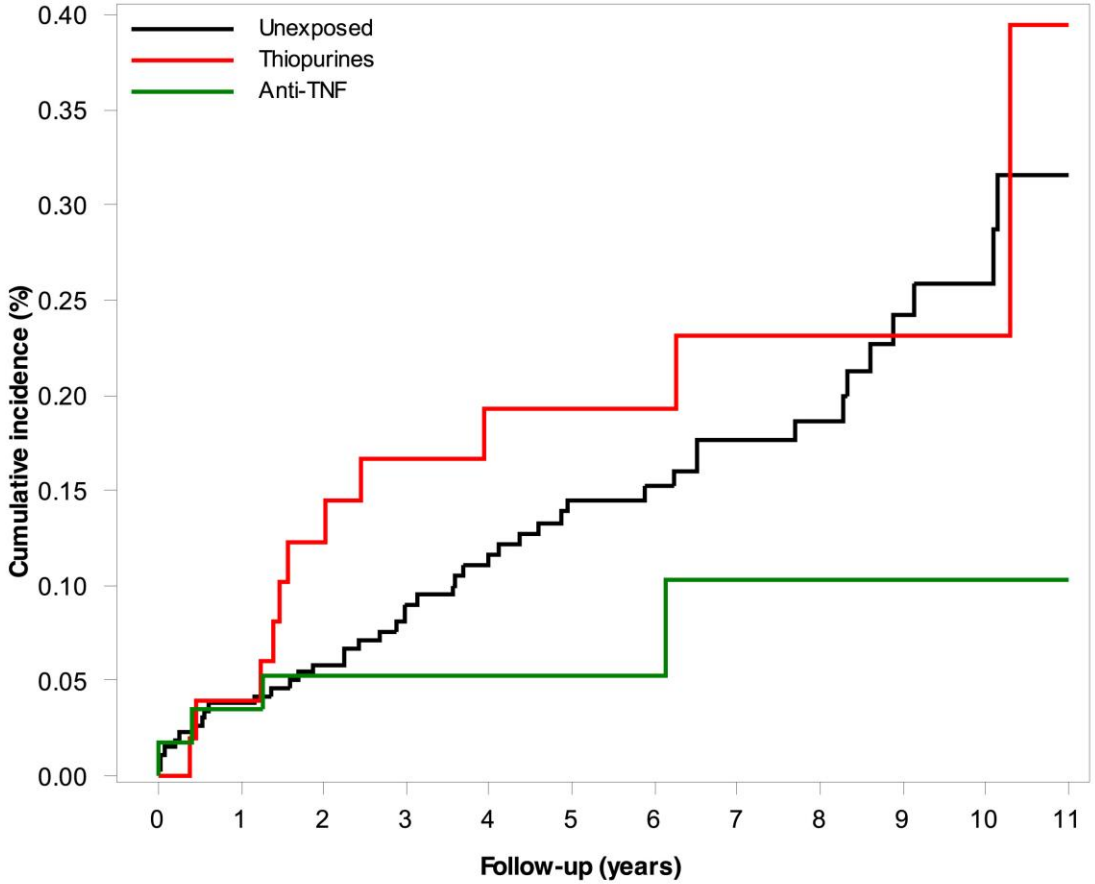
Maternal Exposure to Anti-TNF or Thiopurines for IBD Does Not Increase Risk of Early-life Malignancy in Children

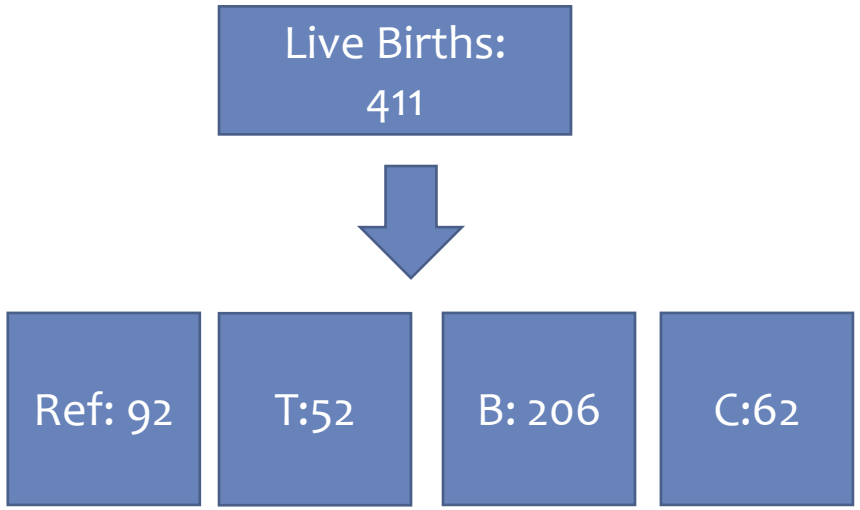


Number at risk

Unexposed	26092	26051	23671	21099	18548	16129	13643	11067	8569	6152	3797	1581
Thiopurines	4994	4988	4617	4213	3793	3278	2768	2244	1717	1168	724	281
Anti-TNF	5725	5721	4941	4190	3432	2740	2096	1533	1049	663	373	129

Antoine Meyer CGH 2023 Sep;21(10):2679-2681.e5

PIANO: Achievement of Developmental Milestones at 12 Months Among Offspring of Women with IBD



In utero exposure to immunomodulator and biologic therapy was not associated with developmental delay compared to unexposed infants or general population.

ASQ-3

Mahadevan, et al. Gastroenterology. 146. S-1, 2014. 10.1016/S0016-5085(14)60001-9.

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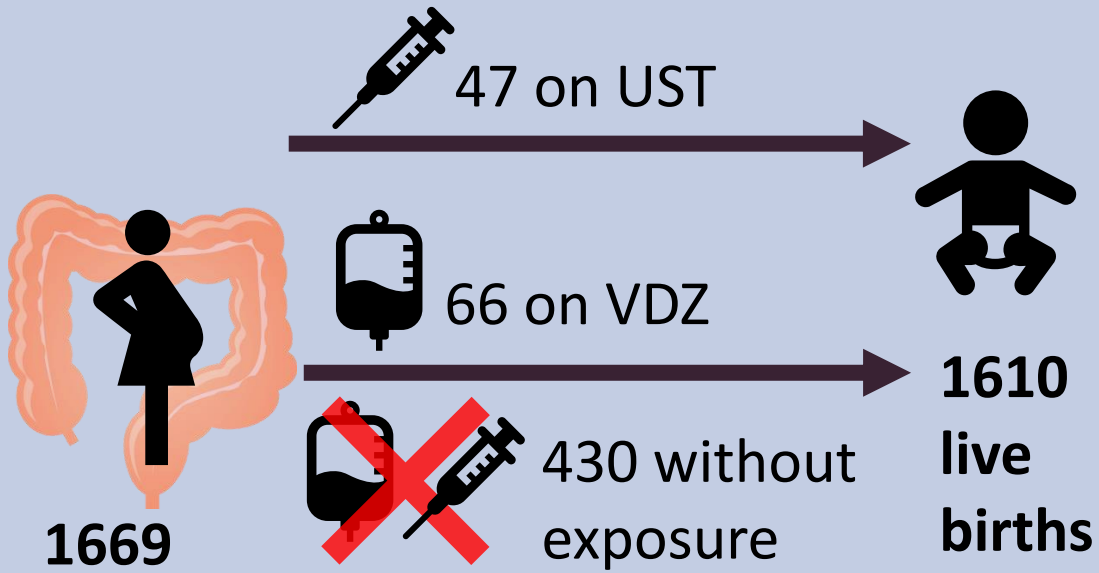
Summary



Pregnancy Outcomes

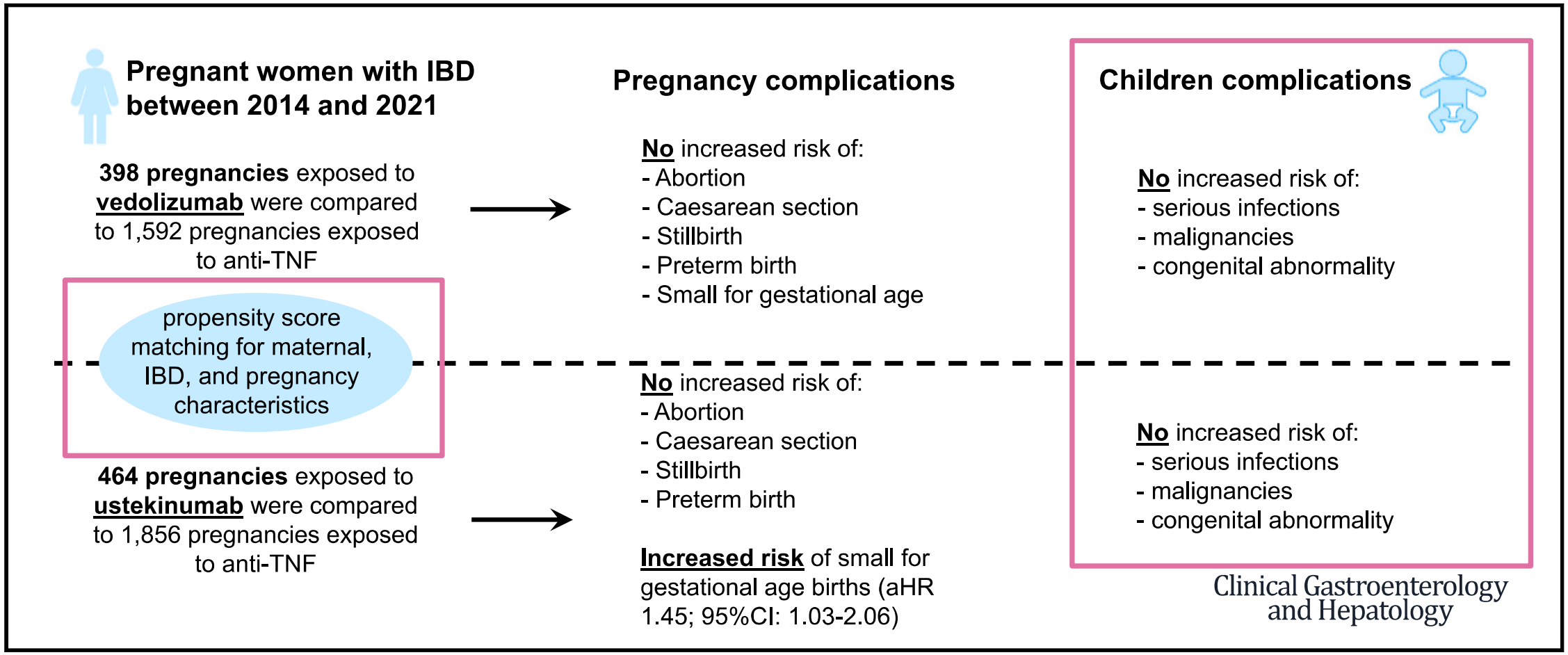
- Preterm birth
- Spontaneous abortion
- Small for gestational age
- Intrauterine growth restriction
- C-section
- Placental complications

Infant Outcomes

- Low Birth Weight
- NICU stay
- Congenital malformations
- Infections at 1 year

Chugh et al Am J Gastro 2204 Mar 1:119(3):468-476

Vedolizumab & Ustekinumab



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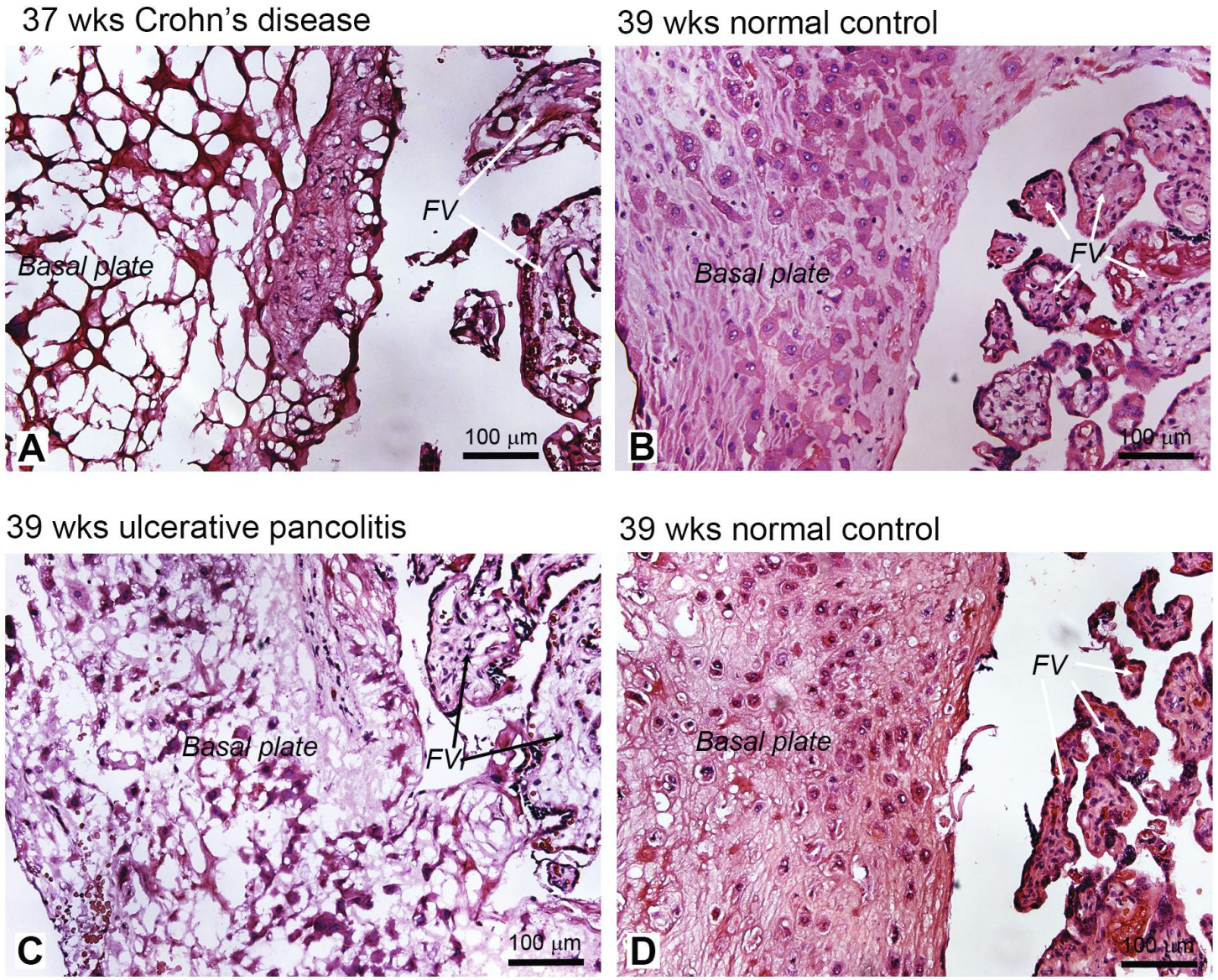
Meyer A, et al. Clin Gastroenterol Hepatol. 2024 Jan 8

Does Vedolizumab treatment during pregnancy alter placental morphology?

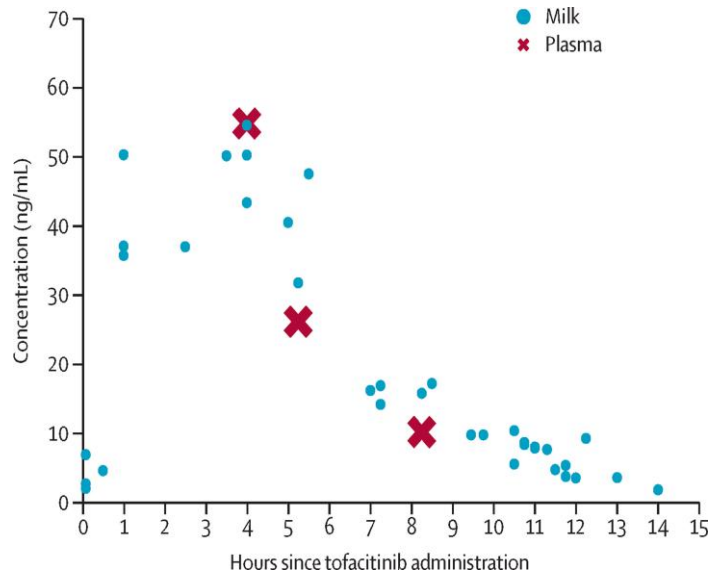


Blaisdell et al. 2022. Inflamm Bowel Dis.

Small Molecules

	Tofacitinib	Upadacitinib	Ozanimod
Animal Reprotox: Feticidal, teratogenic Rats, Rabbits	73x and 6.3x [10 mg BID]	1.6x, 15x [15 mg QD] **0.8x, 7.6x [30 mg QD]** 0.6x, 5.6x [45 mg QD]	0, 0.2, 1, or 5 mg/kg/day 60x, 2x [0.92 mg]
Human Data (maternal)	85 (16 IBD)	54 exposures[2]	78 (20 IBD)[3] exposures
Pregnancy	Avoid, ? lowest dose	Avoid, ? 15 mg dose	Avoid
Lactation	No[1]	No	No

At least 4 weeks between stopping therapy and attempting conception



1. Julsgaard Lancet Gastro Hep 2023
2. Package insert
3. Dubinsky Inflamm Bowl Dis *in press*

Pregnancies in the tofacitinib overall and UC clinical programs

- In the **overall global tofacitinib clinical program**,[a] a total of 184 pregnancies were identified:
  - Maternal exposure: 85
  - Paternal exposure: 99
- There were **40 pregnancies** in the tofacitinib **UC clinical program:**

Maternal exposure

16 cases of maternal exposure

Median age

29.5 years

(range 24–41)

Number of days between the last menstrual period and last tofacitinib dose:

64 and 106 days

Tofacitinib 5 mg BID (2 patients)

6–69 days

Tofacitinib 10 mg BID (12 patients)

Paternal exposure

24 cases of paternal exposure

(included 2 cases from the same patient)

[a]Includes RA, PsA, AS, JIA, UC and PsO clinical programs

AS, ankylosing spondylitis; BID, twice daily; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis

DDW 2024: Mahadevan

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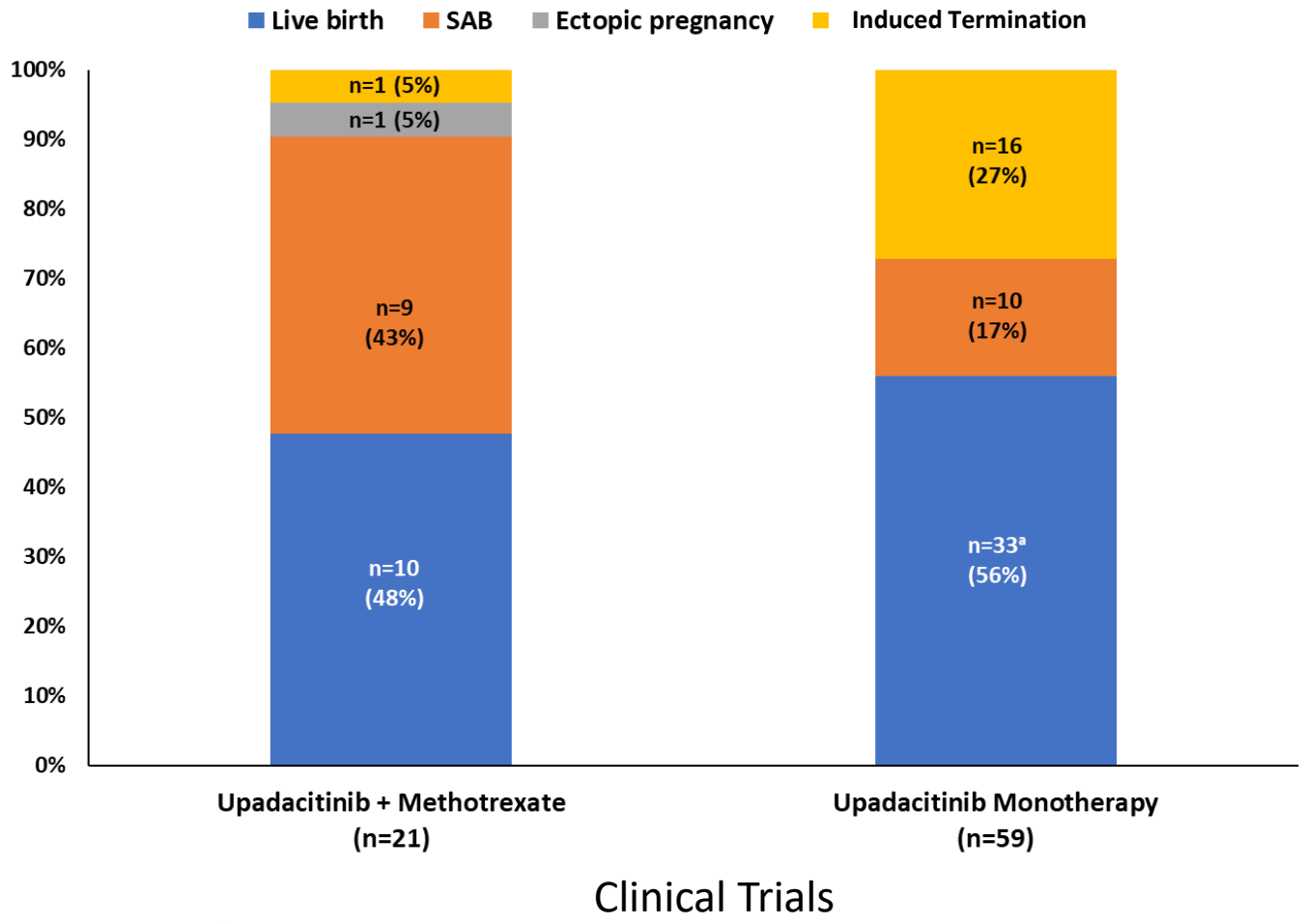
Pregnancy Outcomes in Patients Treated With Upadacitinib: Analysis of Data From Clinical Trials and Postmarketing Reports

N= 128 maternal UPA-exposed pregnancies

- Clinical trials n=80
  - Mean *in utero* exposure 5 wks, 3d
    - Live births (54%)
    - SAB (24%)
    - TAB (21%)
    - Ectopic pregnancy (1%)
    - 1 congenital malformation
      - Atrial septal defect
- Postmarketing cases n=48
  - Live births (46%)
  - Spontaneous abortions (38%)
  - Induced terminations (15%)
  - Ectopic pregnancy (2%)



Mahadevan U Drug Safety *in press*

Levels of Biologics Detected in Breast Milk Are Low and Do Not Adversely Affect Infant Outcomes

1-year post-partum follow-up of 824 women, of whom 75% (n=620) breastfed
Breast milk samples (n=72) collected from patients receiving biologic therapy

Peak concentration (mcg/mL)

- Infliximab—0.74
- Adalimumab—0.71
- Certolizumab—0.29
- Natalizumab—0.46
- Ustekinumab—1.57

Medication detected in breast milk samples from treated women

- Infliximab—66%
- Adalimumab—9.5%
- Certolizumab—23%
- Natalizumab—50%*
- Ustekinumab—67%

* 1 of 2 patients

Rates of infection at 12 months similar in breastfed vs non-breastfed infants

- Any infection, 39% vs 39% in controls (P > .99)

Milestone score

- 87 vs 86 in controls (P = .999)

Breastfeeding while on biologics does not adversely affect infant growth, developmental milestones, or infection rate

Matro R, et al. *Gastroenterology.* 2018;155:696-704.

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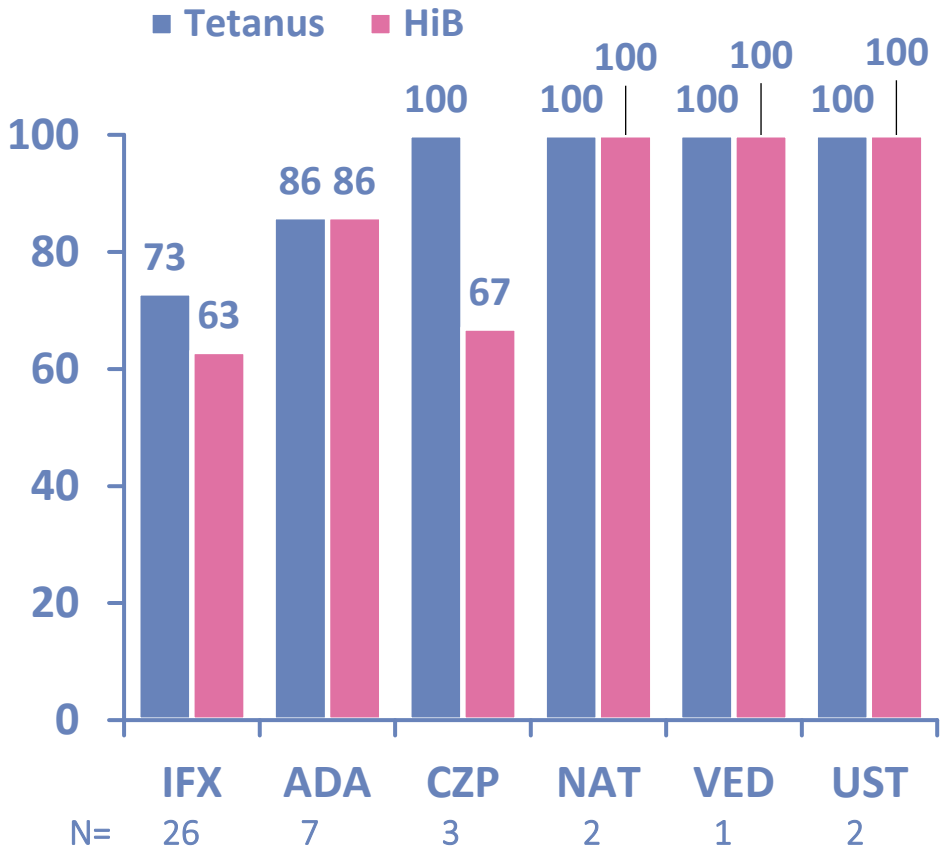
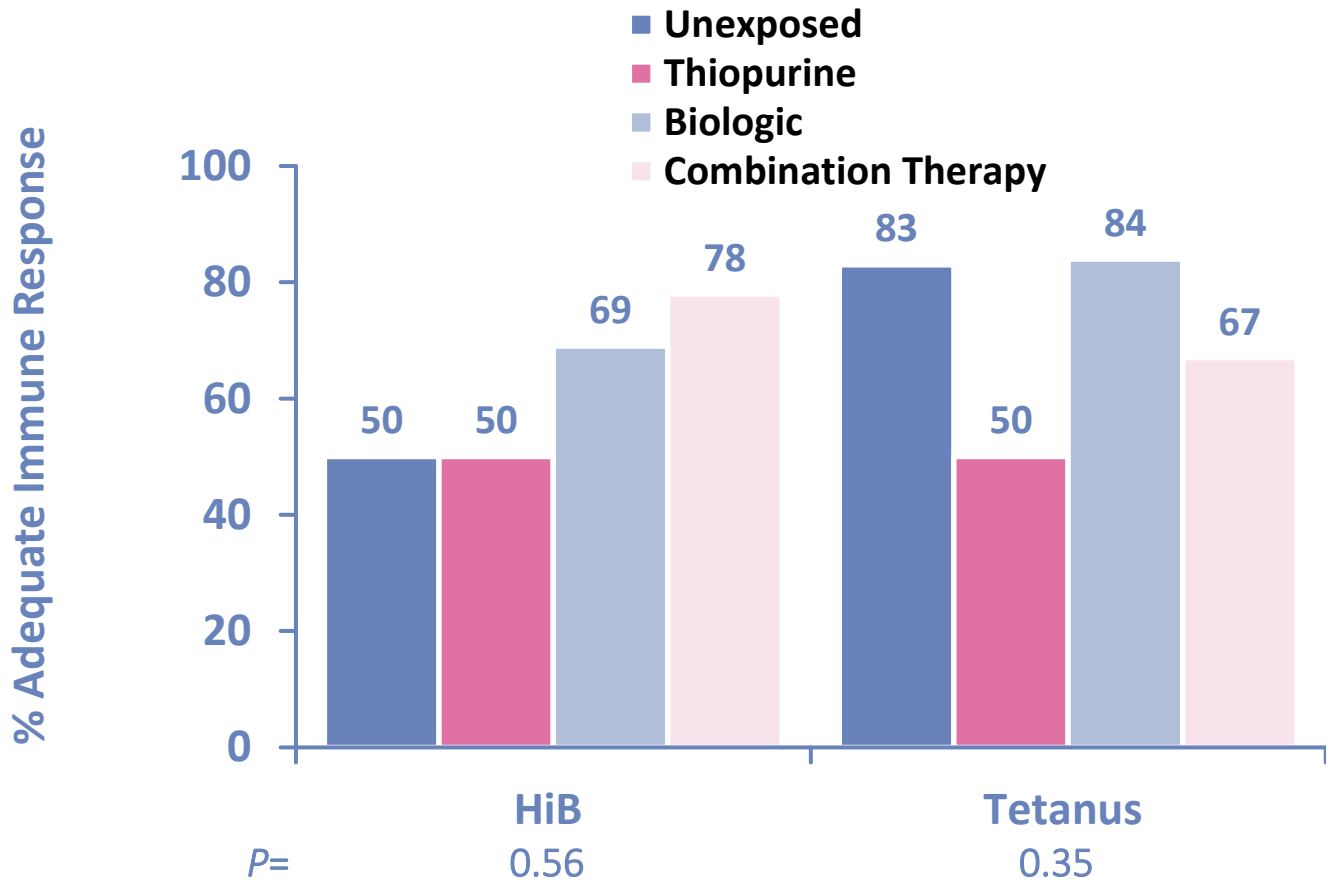
PIANO Registry: Maternal Immunomodulators or Biologics Do Not Impact Vaccine Response

No Difference in Vaccine Response Rate Across Different Biologics



No Difference in Rates of Serologic Response to HiB or Tetanus Groups



Beaulieu, Ananthakrishnan, et al. Clin Gastro Hep, 2017

Rotavirus Vaccination

- 43 biologic exposed infants
  - 2 ADA, 1 CZP reaction unknown
  - 7/40 (17.5%) reaction

Drug	N	Reaction	Type	Levels (µg/ml)
Infliximab	19	6 (32%)	Fever (5) Diarrhea (1)	Diarrhea: 72 (0), 5 (3) NR: 44, 11, 42,28,22. 69
Adalimumab	7	1 (14%)	Fever	No reaction: 14, 7
Certolizumab	12	0	None	No rxn: BLOQ x 5
IFX/CZP	1	0	None	--
Ustekinumab	1	0	None	40

Beaulieu, Ananthakrishnan, et al. Clin Gastro Hep, 2017

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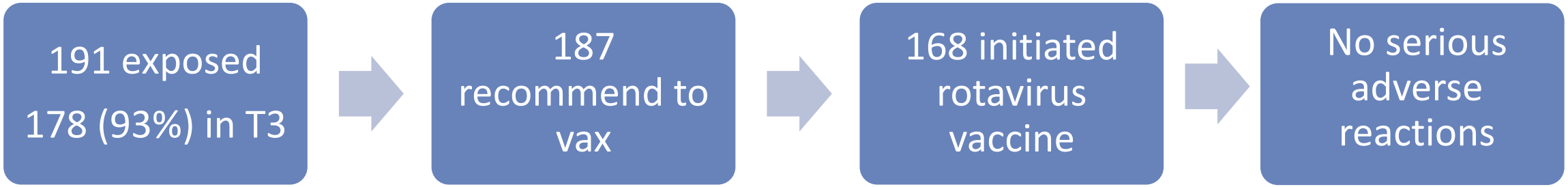
Should Rotavirus Vaccine be given?



- Prospective Canadian Study of infants exposed to biologics in utero
- IFX (67/191 [35%]), ADA (49 [26%]), UST (18 [9%]), VDZ (17 [9%])
- No clinically significant abnormalities in lymphocyte subsets, quantitative immunoglobulins, or mitogen responses
- Authors conclude: "*Lymphocyte subsets and the safety of live rotavirus vaccination are generally not affected by in-utero exposure to biologic agents. Rotavirus vaccination can be offered to infants exposed to anti-TNF agents in utero*"

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T Fitzpatrick Lancet Child Adol Health Volume 7, Issue 9, September 2023, Pages 648-656

BCG vaccination

➢ Systematic review on live vaccines outcome in infants exposed to biologic agents (mainly anti-TNF) *in utero* due to maternal IMIDs

- Total of 215 infants vaccinated with BCG vaccine ≤ 1st year of live (> 80% vaccinated ≤ 6 mths of age)
- **Adverse events** - all reported in infants vaccinated ≤ 6 mths of age

  - **!!! 1 death** at age 4.5 mths - **disseminated BCG infection** (vaccination at 3 mths; exposure to IFX in 3rd trimester due to maternal CD)

  - 7 infants non-serious AE to vaccination (all exposed to IFX) - injection site swelling and/or axillary lymphadenopathy, NO need of anti-TB therapy

Goulden et al., Rheumatology 2022

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Global Consensus Conference

GRADE Recommendations

Continue **5-ASA**	Strong	Low
Continue **Sulfasalazine***	Conditional	Very low
Corticosteroid* therapy when clinically necessary	Conditional	Low
Discontinue **methotrexate***	Strong	Very low
Continue **thiopurine*** -precaution for intrahepatic cholestasis by measurement of liver enzymes, metabolite levels and consideration of split dosing (consensus)	Conditional	Very low
Continue **anti-TNF therapy** on schedule	Conditional	Very low
Continue **vedolizumab** therapy on schedule	Conditional	Very low
Continue **ustekinumab** therapy on schedule	Conditional	Very low

**Sulfasalazine, corticosteroids, methotrexate and thiopurines are not FDA approved for the treatment of IBD*

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Consensus

Pregnant women with IBD with active disease should **start or optimize appropriate IBD** therapies as in nonpregnant patients with the exception of thiopurines, methotrexate, jak inhibitors and S1P modulators
Women with IBD who are pregnant or attempting conception should continue **biosimilars** to existing biologics
Women with IBD who are pregnant or attempting conception should continue **anti-IL-23** therapy throughout pregnancy (mirikizumab, risankizumb, guselkumab)
Women with IBD should **discontinue ozanimod** at least 3 months prior to conception unless there is no effective alternative therapy to maintain maternal health
Women with IBD should **discontinue etrasimod** at least 1-2 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health
Women with IBD should **discontinue tofacitinib, upadacitinib, filgotinib** at least 4 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health

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GRADE

Inactive vaccines in children born to mothers with IBD on anti-TNF agents • comparable efficacy vs. unexposed • Comparable safety/adverse events vs. unexposed	 Strong Conditional	Very low
We suggest that **live rotavirus** vaccine may be provided in children with in-utero exposure to anti-TNF	Conditional	Very low
We recommend that **live BCG vaccine** be avoided in the first 6 months* of life in children with in-utero exposure to anti-TNF due to risk of disseminated TB and associated mortality	Strong	Very low

Consensus

Inactive vaccines should be **given on schedule** to infants of women with IBD regardless of in utero IBD medication exposure
Children exposed to jak inhibitors or S1P modulators in utero may receive live vaccines after 1 month

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Questions?