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Pregnancy in IBD And Neonatal Outcomes

Global Consensus for the Management of IBD in Pregnancy

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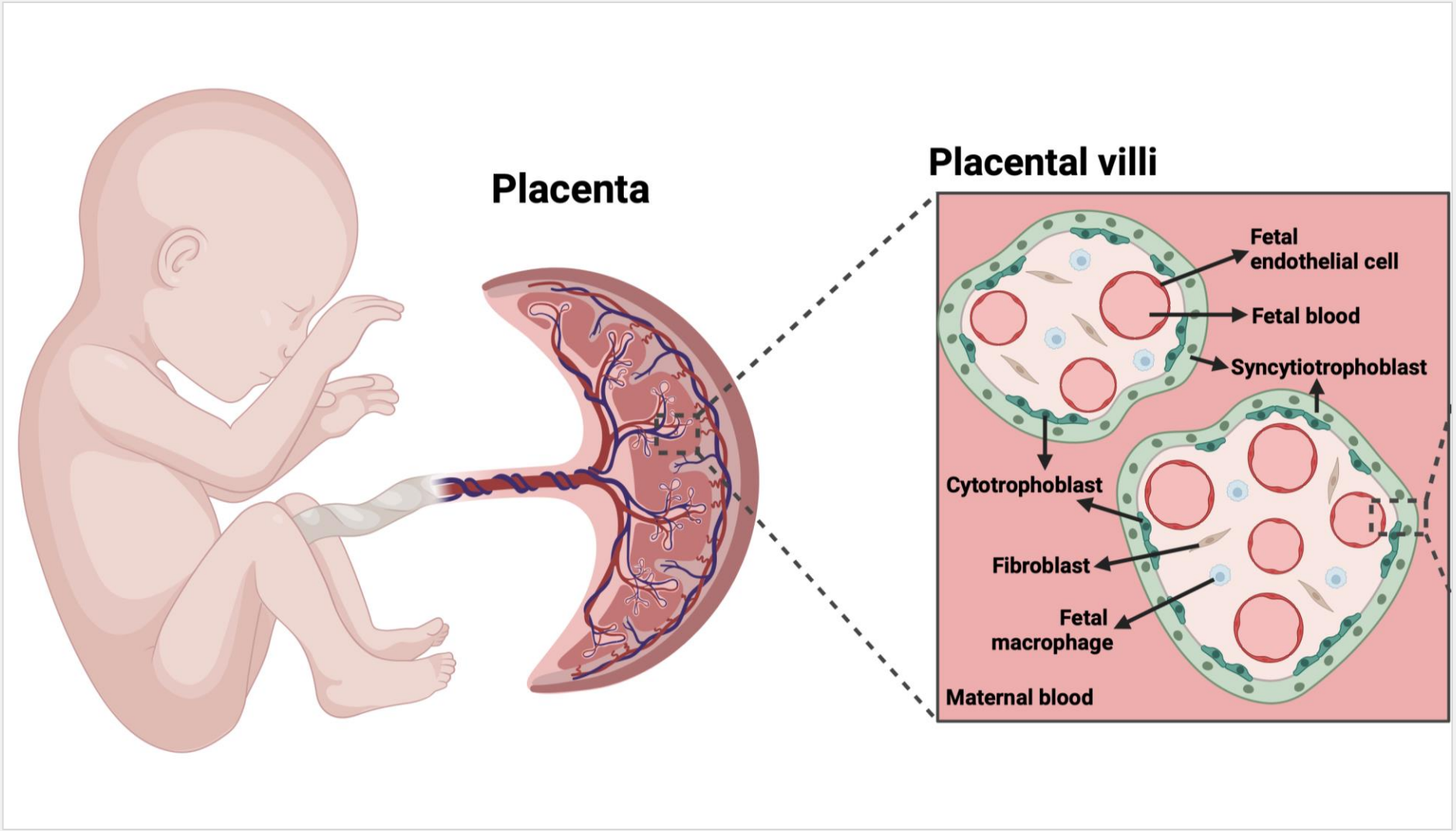
IBD is often diagnosed during the reproductive years, making it essential to understand its **effects on fertility, pregnancy, and childbirth outcomes**.

Pregnancy represents a period of intense metabolic, hormonal, microbiome and immunological changes.

For women with immune-mediated diseases like IBD, this **can increase the risk of pregnancy complications**, in part due to the unique role of the placenta.

https://urldefense.com/v3/__https:/www.nature.com/nrrheum__;!!LQC6Cpwp!rAgdlwf4ndvYlFOuQrFpVU79uAt2lmcxxkC2tyixkfW_YPgF_ynN6bFTvLhrmuzstzOxU9ZWkYPkwCYPAsrynlOhFx0$"Nature Reviews Rheumatology ***volume 16****, pages113–122 (2020).*



The placenta

expresses an equal complement of maternal and paternal genes without eliciting a maternal immune response that rejects the organ.

Image credit: PIANO. PIANO Global Consensus. Accessed September 10, 2024, 2024.

There are **limited human data** on the safety of new therapies during pregnancy.

For IBD patients, **stopping medication increases disease activity**, leading to higher risks of maternal and fetal complications.[1]

Mahadevan U, Long MD, Kane SV, et al. Pregnancy and Neonatal Outcomes After Fetal Exposure to Biologics and Thiopurines Among Women With IBD. Gastroenterology. Mar 2021;160(4):1131-1139. doi:10.1053/j.gastro.2020.11.038

Background: Global Consensus Group

Universal guidelines with consistent interpretation of data and sensitivity to regional differences

Healthcare professionals and patient advocates from around the globe

Follows GRADE and RAND methodologies

Funding: Helmsley Charitable Trust

Embargo date: August 22, 2025

Journals:

1. Clinical Gastroenterology and Hepatology
2. Gut
3. American Journal of Gastroenterology
4. Inflammatory Bowel Diseases
5. Journal of Crohn's Colitis
6. Alimentary Pharmacology and Therapeutics

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Clinical Gastroenterology and Hepatology 2025;■:■–■

Global Consensus Statement on the Management of Pregnancy in Inflammatory Bowel Disease

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Cynthia Seow
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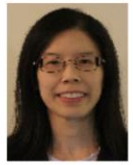

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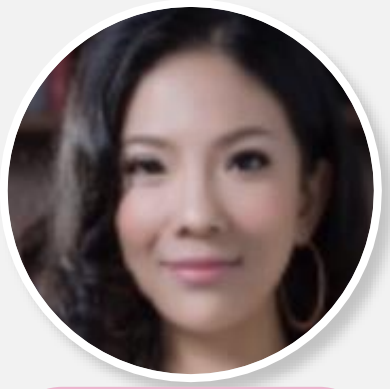

Taiwan

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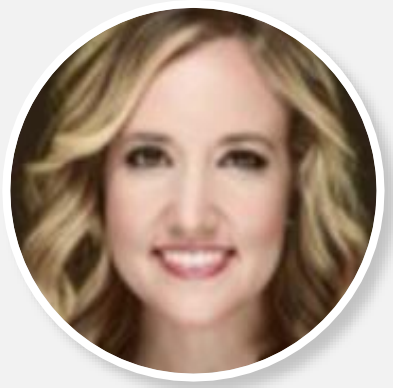


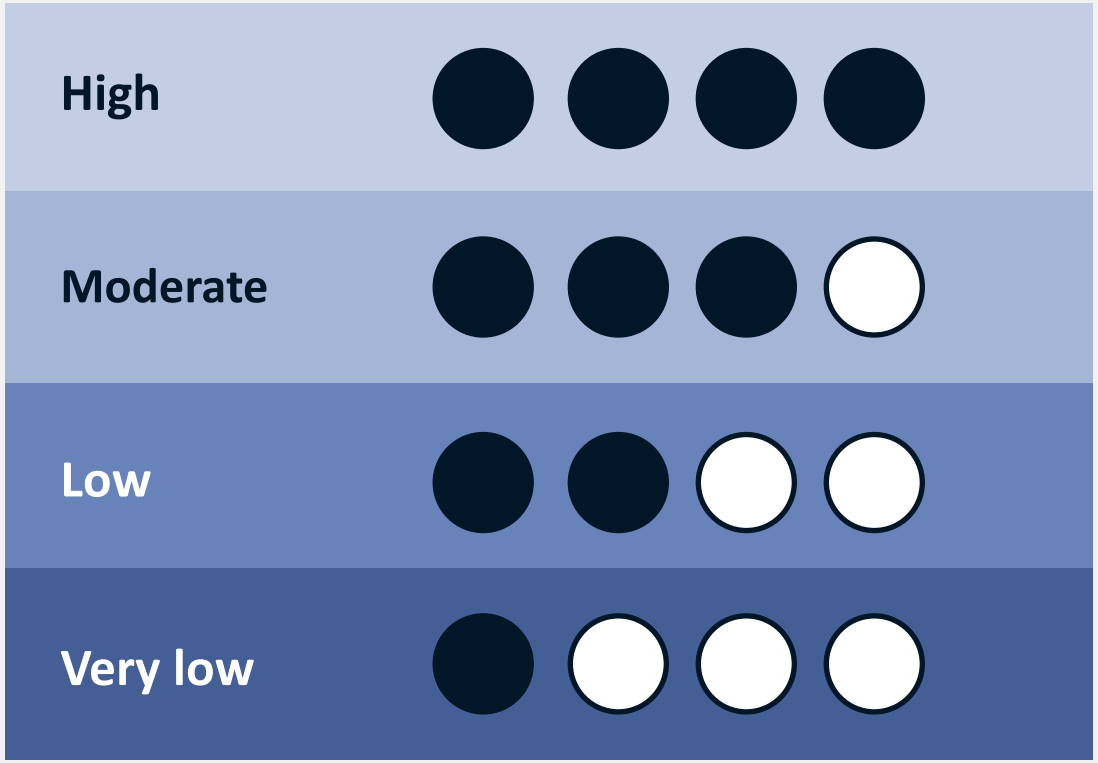
USA

GRADE

Universal grading for evidence: **High, Moderate, Low, Very Low**

Recommendations rated: **Strong** (benefits > risks) or **Conditional** (uncertainty)

Implications: A strong recommendation means most patients would prefer the suggested action, and clinicians should generally offer it

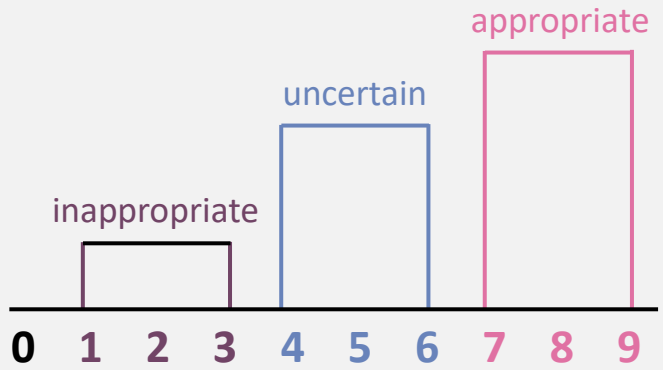


Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. Apr 2011;64(4):383-94. doi:10.1016/j.jclinepi.2010.04.026

RAND Consensus Panel

Applied when **GRADE data** are unavailable

Combines **evidence + expert opinion**



RAND Disagreement Index (DI)

<1.0 = general agreement

≥1.0 = extreme variation

FItch K BS, Aguilar MD, Bernard B, LaCalle JR, Lazaro P, van het Loo M, McDonnell J, Vader JP, Kahan JP. The RAND/UCLA Appropriateness Method User's Manual. RAND; 2001

Maternal factors impacting pregnancy

Fertility

Pre-conception counseling and optimization

Management of disease activity during pregnancy

Management of pregnancy

IBD medications during pregnancy

IBD medications during lactation

Pregnancy adverse events

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GRADE Statement 1:

We suggest counseling that children with first degree relatives with IBD, as compared to those without, have an increased risk of development of IBD.

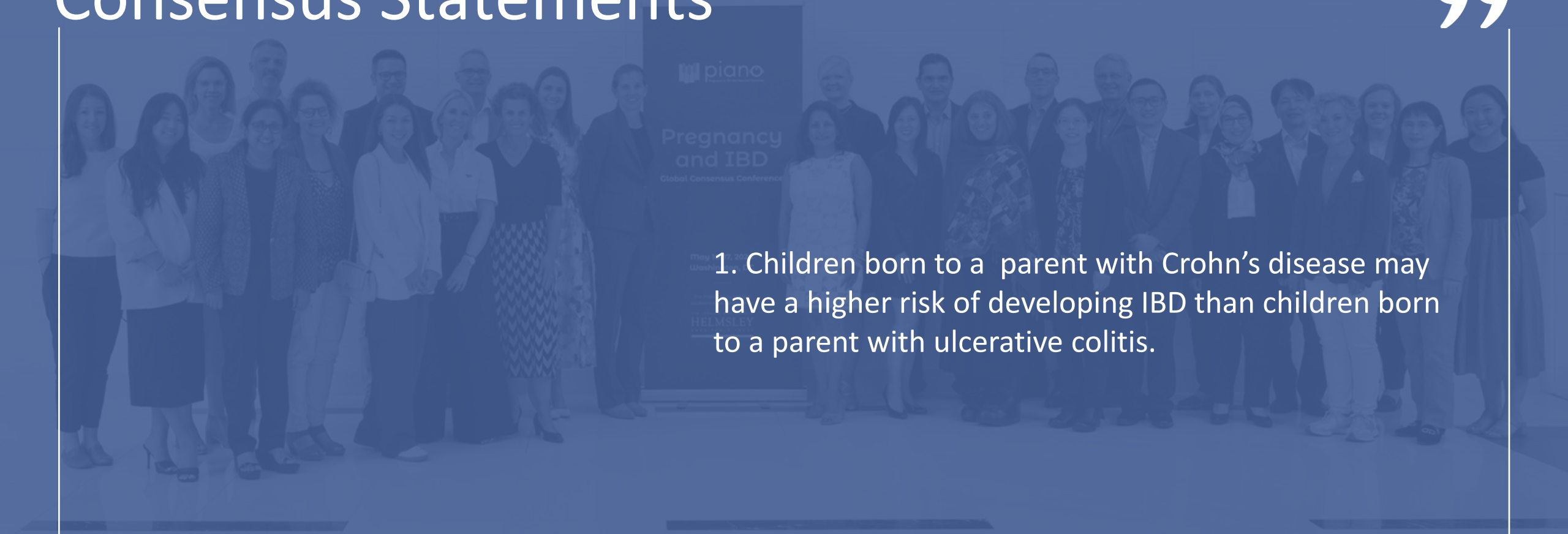
Level of Evidence:

Low

Recommendation:

Conditional

Consensus Statements



1. Children born to a parent with Crohn's disease may have a higher risk of developing IBD than children born to a parent with ulcerative colitis.

Does Maternal Inflammation in Pregnancy Affect Placental Function in Women with IBD?

Abnormal placentation is linked to major obstetrical complications.

Maternal inflammation affects placental function and raises the risk of miscarriage, preterm birth, and small-for-gestational-age infants.

It is likely that IBD negatively affects development or function of the placenta.

What Increases IBD Risk in Offspring

- Antibiotics
- Diet
- Maternal Microbiome

What is the Impact of Prenatal Antibiotics Use on IBD Risk in Offsprings? *Body of Evidence (Clinical studies)*

Meta-analysis by Agrawal (2021)

- 2 high-quality studies, 1 cohort and 1 case-control
- **Yes. Risk of IBD with maternal antibiotics → OR 1.75 (1.22-2.51)**

Swedish population-based study (2019)

- **Risk of very early onset IBD with intra-uterine antibiotic exposure → adjusted HR 1.93 (1.06-3.50)**
- Risk of VEO CD with intra-uterine antibiotic exposure → aHR 2.48 (1.01-6.08)
- But not risk of VOE UC with intra-uterine antibiotic exposure → aHR 1.25 (0.47-3.26)

Danish population-based study (2023)

- Risk of IBD with maternal **exposure to ≥3 courses of antibiotics in** pregnancy → **aHR 1.29 (1.03-1.62)**
- Risk of UC → aHR 1.45 (1.06-2.00)
- But not risk of CD → aHR 1.15 (0.83-1.60)

Agrawal et al. EClinicalMedicine 2021
Ortqvist et al. Gut 2019
Agrawal et al. Gut 2023

Does a Western Diet in IBD Mothers Affect IBD Risk in Offspring?

2 preclinical studies show maternal western diets → increased risk of IBD in offspring

MOMMY-IBD study (2024) – 3 sites in Hong Kong & Mainland China

- IBD mothers had higher food additive (FA) intake than non-IBD mothers
- FA intake associated with depletion in *Bacteroides spp.,* and enrichment in *Streptococcus spp*. in mothers with IBD
- **Fecal calprotectin significantly higher in the gut of infants born to mothers with higher FA intake in IBD and non-IBD groups**

MELODY Interventional trial (2020, ongoing)

- Impact of an "IBD-anti-inflammatory diet (AID)" on the microbiome of pregnant IBD women and the newborn microbiome

Huang et al. Microbiome 2023
Xie et al. Front Immunol 2018
Gilat et al. Scand J Gastroenterol 1987
Zhang et al. DDW 2024
Peter et al. Contemp Clin Trials Commun 2020

Does Maternal Microbiome Impact Pregnancy and/or Risk of IBD in Offspring?

MECONIUM study (2020) – Mount Sinai

- Abnormal gut microbiota composition persisted in mothers with IBD during pregnancy
- Associated with changes in bacterial diversity and bacteria species in the infant's stool

MOMMY-IBD study (2024)– 3 sites in Hong Kong & Mainland China

- Altered gut bacteria/virome/ fungi in IBD mothers during pregnancy and up to 18 months postpartum
- **Reduced "commensal" bacteria strain sharing in IBD mothers and their infants**
- **Cesarean sections and maternal antibiotic exposure** led to decreased vertical transmission of bacterial communities in infants

One preclinical intervention study (2022)

- Maternal *Lactobacillus reuteri* supplementation shifts intestinal microbiome in mice
- Provides protection from experimental colitis in female offsprings

Torres et al. Gut 2020
Tun et al. DDW 2024
Krishna et al. FASEB Bioadv 2022

Maternal factors impacting pregnancy

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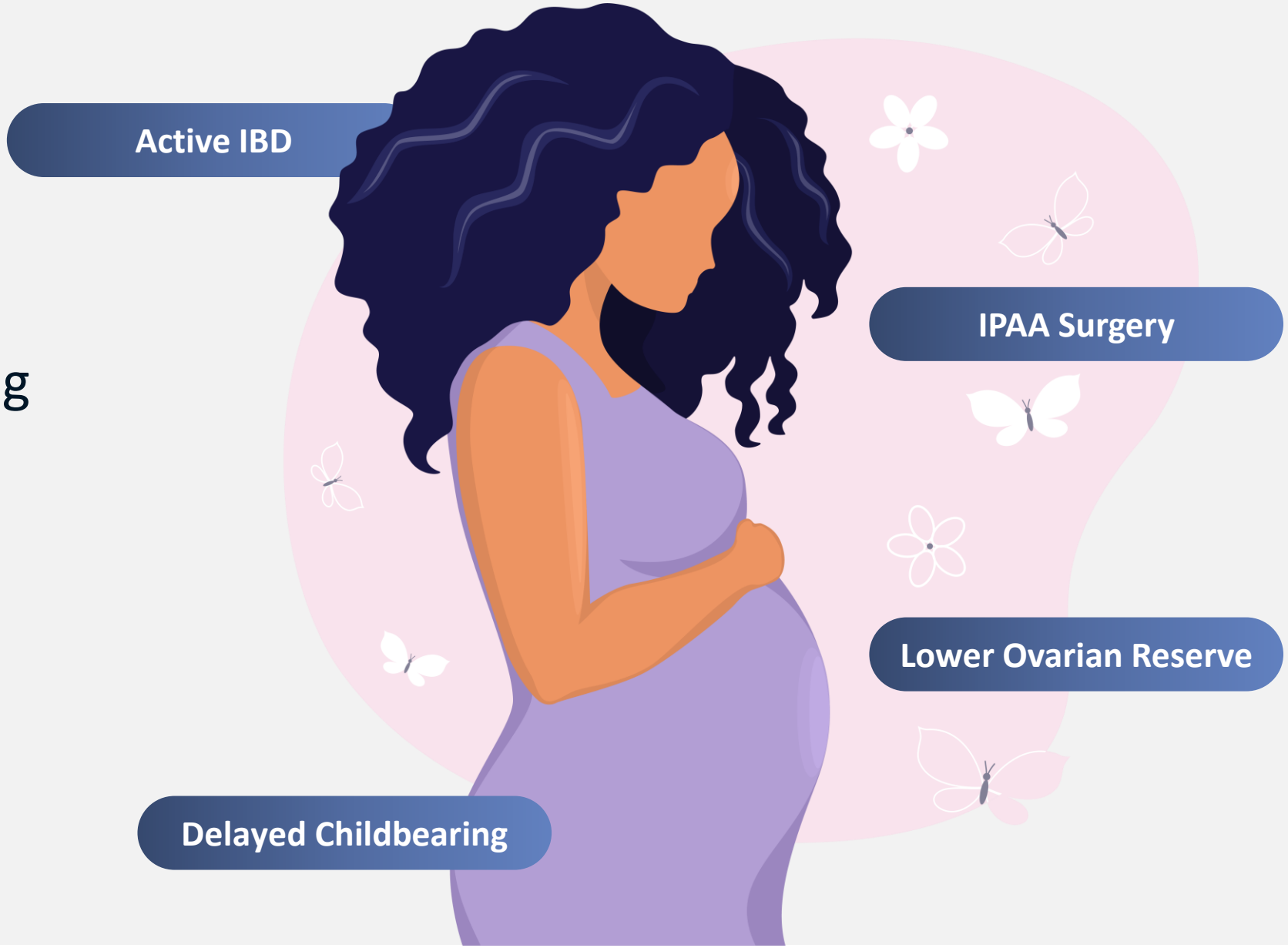
Key factors contributing to reduced fertility in women with IBD



GRADE Statement 2:

We suggest counseling that women with IBD may have decreased fertility compared to women without IBD.

Level of Evidence:
Very Low

Recommendation:
Conditional

GRADE Statement 3:

In women with ulcerative colitis, we suggest counseling that prior ileal pouch anal anastomosis is associated with decreased fertility when compared to women with ulcerative colitis who have not had ileal pouch anal anastomosis.

Level of Evidence:
Very low

Recommendation:
Conditional

GRADE Statement 4:

In women with IBD, we recommend counseling that active disease increases the risk of infertility as compared to inactive disease.

Level of Evidence:
Very low

Recommendation:
Strong

GRADE Statement 5:

We suggest counseling that women with IBD may have comparable effectiveness of assisted reproductive technology when compared to women without IBD, as measured by live birth .

Level of Evidence:

Very low

Recommendation:

Conditional

GRADE Statement 6:

We suggest counseling that women with IBD who have undergone pelvic surgery with IBD have similar effectiveness of in vitro fertilization when compared to women without IBD, as measured by live birth.

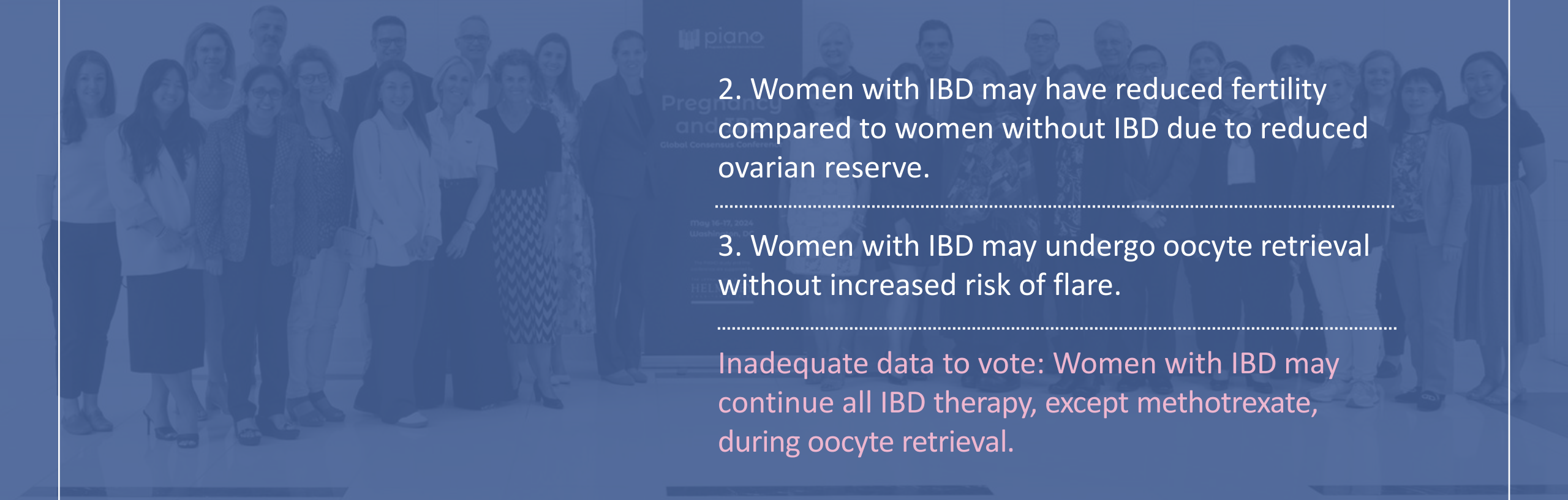
Level of Evidence:

Very low

Recommendation:

Conditional

Consensus Statements



2. Women with IBD may have reduced fertility compared to women without IBD due to reduced ovarian reserve.

3. Women with IBD may undergo oocyte retrieval without increased risk of flare.

Inadequate data to vote: Women with IBD may continue all IBD therapy, except methotrexate, during oocyte retrieval.

Maternal factors impacting pregnancy

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GRADE Statement 7:

We recommend that women with IBD undergo preconceptional counseling.

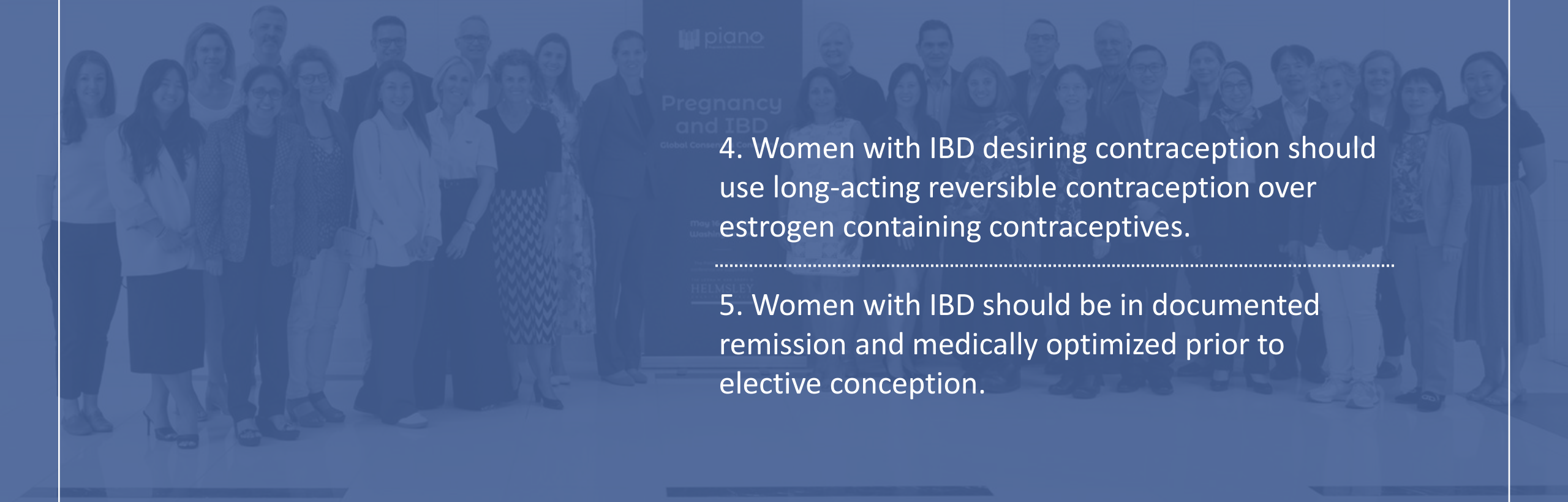
Level of Evidence:

Low

Recommendation:

Strong

Consensus Statements



4. Women with IBD desiring contraception should use long-acting reversible contraception over estrogen containing contraceptives.

5. Women with IBD should be in documented remission and medically optimized prior to elective conception.

Contraception Options

1

Barrier methods: Least effective but protects against STIs (sexually transmitted infections).

2

Oral contraceptives:

- **Combined (estrogen + progesterone)**: Increased risk of VTE (venous thromboembolism), human error, and absorption issues.
- **Progesterone-only**: No increased VTE risk but still affected by human error and absorption.

3

Long-Acting Reversible Contraception (LARCs):
Most effective, no estrogen, no increased risk of VTE.

Pre-conception counseling and recommendations

- Cessation of substances
- Stop teratogenic medications
- Achieve disease remission (3-6 months prior to conception)
- Nutritional assessment and prenatal vitamins
- Weight management
- Vaccinations
- Preconception Maternal Fetal Medicine
- IBD treatment plan
- Fertility Specialist
- Physical activity

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GRADE Statement 8:

We suggest that urgent and emergent IBD surgery during pregnancy be completed when required, and not based on trimester.

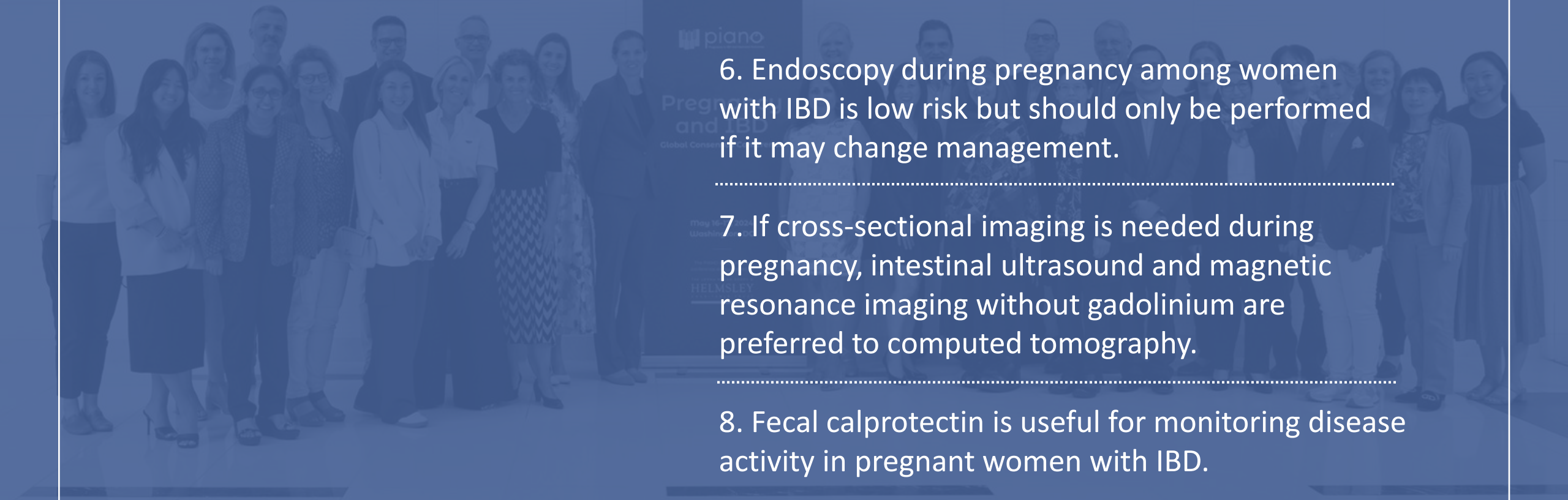
Level of Evidence:

Very low

Recommendation:

Conditional

Consensus Statements



6. Endoscopy during pregnancy among women with IBD is low risk but should only be performed if it may change management.

7. If cross-sectional imaging is needed during pregnancy, intestinal ultrasound and magnetic resonance imaging without gadolinium are preferred to computed tomography.

8. Fecal calprotectin is useful for monitoring disease activity in pregnant women with IBD.

	Assessment of Disease Activity	Comment
Laboratory Tests	Serum Inflammatory markers C Reactive Protein, Sedimentation Rate	Can be elevated from pregnancy
	Fecal Calprotectin	Effective for monitoring in pregnancy
	Serum Drug Concentrations	May vary in pregnancy
Cross-sectional imaging	Intestinal Ultrasound	Low risk: Accurate in trimester 1,2 but technically challenging in trimester 3
	Computed Tomography	Relatively safe. The cumulative radiation exposure of a single CT scan (~ 50 mGy) is below the level of concern
	Magnetic Resonance Imaging	Low risk. Avoid gadolinium (potential teratogen) during first trimester
Procedures	Endoscopy	Low risk: Can be performed if indicated and will change management
	Surgery	Perform if indicated regardless of trimester. Should be done at expert centers Indications: acute refractory colitis, perforation, abscess, refractory hemorrhage, bowel obstruction

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GRADE Statement 9:

We suggest that pregnant women with IBD take low dose aspirin by 12-16 weeks gestation to prevent preterm pre-eclampsia.

Level of Evidence:

Low

Recommendation:

Conditional

GRADE Statement 10:

We suggest that pregnant women with Crohn's disease and active perianal disease undergo cesarean delivery.

Level of Evidence:

Very low

Recommendation:

Conditional

GRADE Statement 11:

We suggest that pregnant women with IBD and prior ileal pouch anal anastomosis consider cesarean delivery.

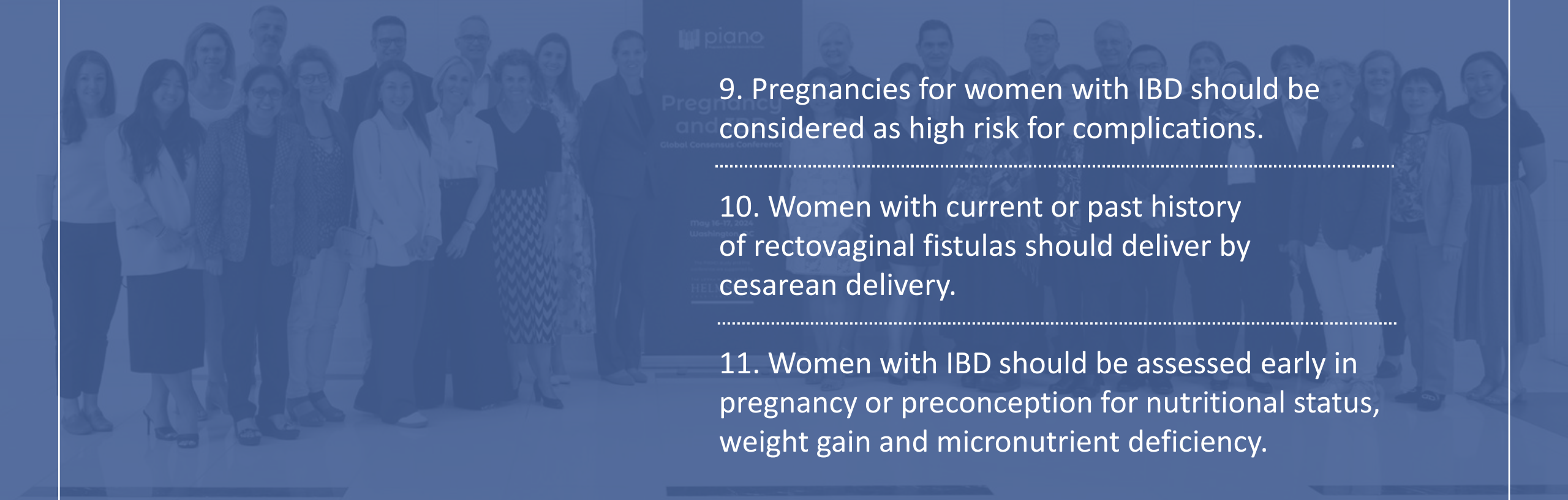
Level of Evidence:

Very low

Recommendation:

Conditional

Consensus Statements



9. Pregnancies for women with IBD should be considered as high risk for complications.

10. Women with current or past history of rectovaginal fistulas should deliver by cesarean delivery.

11. Women with IBD should be assessed early in pregnancy or preconception for nutritional status, weight gain and micronutrient deficiency.

Pre-eclampsia is one of the leading causes of maternal and perinatal morbidity and mortality.

Women with IBD may have an increased risk of preterm pre-eclampsia.

Low dose aspirin may prevent pre-eclampsia in at-risk patients.

Boyd et al, PLOS One, 2015
Tarar et al, Int J Colorectal Dis, 2022
Rolnik et al NEJM, 2017, Duley et al, Cochrane Database Syst Rev, 2019, Boyd et al PLOS One, 2015, Prakash et al Inflamm Bowel Dis, 2023, Stephansson et al, Clin Gastroenterolo Hepatol, 2010, Tandon et al Aliment Pharmacol Ther, 2020, Patel et al, Inflamm Bowel Dis, 2021, DeBolt et al, Dig Dis Sci. 2024, Yu et al, ACG ASM, 2023.

Low dose aspirin may prevent pre-eclampsia in at-risk patients

ASPRE study

- RCT: aspirin at a dose of 150 mg/day, from 11-14 36 weeks of gestation given to women at high-risk for preterm pre-eclampsia*
- ASPRE study 13/798 (aspirin) vs 35/822 (placebo), **aOR 0.38 [0.2-0.7]**
- Women at high risk of preeclampsia without IBD benefit from low dose aspirin started ≤16 weeks

No evidence of Increased risk of IBD flare in women taking low dose aspirin

- Retrospective cohort studies only

Must be started by week **12-16 gestation**

Consideration for stopping at **week 36** to reduce risk of bleeding

** maternal factors, mean arterial pressure, uterine-artery pulsatility index, and maternal serum pregnancy-associated plasma protein A and placental growth factor*

Rolnik et al NEJM, 2017, Duley et al, Cochrane Database Syst Rev, 2019, Boyd et al PLOS One, 2015, Prakash et al Inflamm Bowel Dis, 2023, Stephansson et al, Clin Gastroenterolo Hepatol, 2010, Tandon et al Aliment Pharmacol Ther, 2020, Patel et al, Inflamm Bowel Dis, 2021, DeBolt et al, Dig Dis Sci. 2024, Memel et al Am J of Gastroenterol 2024

Women with IBD may have an increased risk of preterm **pre-eclampsia**

Pre-eclampsia (PE) typically affects 2%–5% of pregnant women and is one of the leading causes of maternal and perinatal morbidity and mortality

Danish National Birth Cohort (>85,000 women) 1996-2002

- CD 278, UC 388
- Overall preeclampsia rate not elevated HR 1.21 [0.76-1.95]
- Severe preeclampsia elevated in women with IBD **HR 2.24** [1.05-4.8]

National inpatient survey (US 2016-2018)

- 8,079,828 pregnancies (CD 8,475, UC 5,665)
- CD preeclampsia / eclampsia **aOR 1.52 [1.15-2.02]**
- UC preeclampsia / eclampsia aOR 1.05 [0.68-1.64]

Boyd et al, PLOS One, 2015
Tarar et al, Int J Colorectal Dis, 2022

What does “high risk pregnancy” mean in different health care environments?

- Specialist IBD pregnancy clinics
- Maternal-Fetal medicine clinics
- Education for midwives concerning risks and what to look for

Caesarean delivery for women with prior IPAA

Conflicting data on the impact of vaginal delivery in women with IPAA

Systematic review of 8 studies (358 patients) – no difference in pouch function except for complicated VD

One study showed reduced squeeze pressure, more sphincter defects and worse QoL in women having VD compared to CS

Foulon et al, Inflamm Bowel Dis, 2017, Remzi et al Dis Colon Rectum, 2005.

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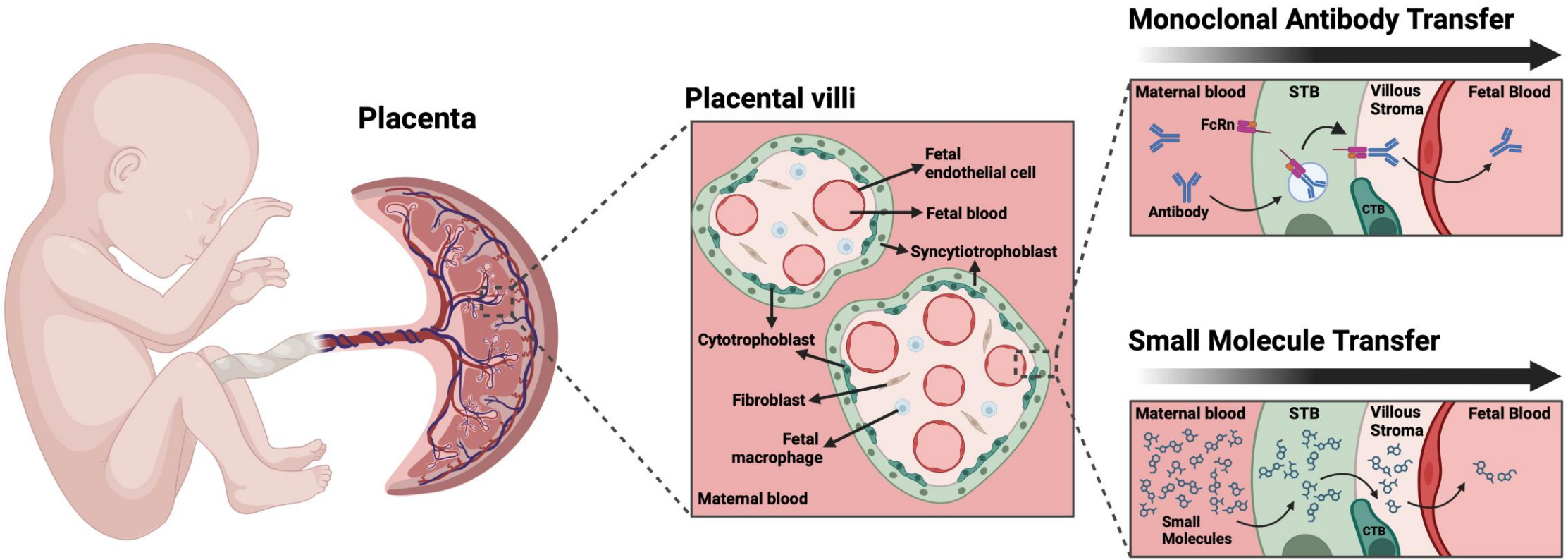
Evolving guidelines emphasize controlling disease activity for both maternal and fetal health.

Yet taking IBD medications have limited safety data for mother and child.

Deescalating therapy or stopping biologics before the third trimester led to more disease flares.

Medications in Pregnancy

1	Pregnant women are not included in IBD clinical trials
2	Unmeasured confounding is innate to uncontrolled studies
3	Existing disease activity impacts decision to continue or discontinue therapy – the decision is not random!
4	Low event rates for adverse events
5	Small cohort sizes
6	Congenital malformations occur in 5-8% of all births
7	Preterm birth (9.9% of births) predisposes to neonatal infection


Placenta
Placental villi
Fetal endothelial cell
Fetal blood
Syncytiotrophoblast
Cytotrophoblast
Fibroblast
Fetal macrophage
Maternal blood
Monoclonal Antibody Transfer
Maternal blood
STB
Villous Stroma
Fetal Blood
FcRn
Antibody
CTB
Small Molecule Transfer
Maternal blood
STB
Villous Stroma
Fetal Blood
Small Molecules
CTB

GRADE Statement 12:
For women with IBD who are pregnant or attempting conception, we recommend continuing maintenance 5-aminosalicylate therapy.

Level of Evidence: Low

Recommendation: Strong

GRADE Statement 13:
In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance sulfasalazine therapy.

Level of Evidence: Very Low

Recommendation: Conditional

GRADE Statement 14:
In women with IBD who are pregnant, we suggest use of corticosteroid therapy when clinically necessary with appropriate monitoring.

Level of Evidence: Low

Recommendation: Conditional

GRADE Statement 15:
In women with IBD we recommend discontinuing maintenance methotrexate therapy prior to conception.

Level of Evidence: Very Low

Recommendation: Strong

GRADE Statement 16:
In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance thiopurine therapy as data does not demonstrate an increased risk of congenital malformations or infant infections.

Level of Evidence: Very Low

Recommendation: Conditional

GRADE Statement 17:

In women with IBD who are pregnant or attempting conception, we recommend continuing maintenance anti-tumor necrosis factor therapy throughout pregnancy.

Level of Evidence: Low

Recommendation: Strong

GRADE Statement 18:

In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance combination therapy with an anti-tumor necrosis factor and thiopurine therapy throughout pregnancy.

Level of Evidence: Very low

Recommendation: Conditional

GRADE Statement 19:

In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance vedolizumab therapy throughout pregnancy.

Level of Evidence: Low

Recommendation: Conditional

GRADE Statement 20:

In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance ustekinumab therapy throughout pregnancy.

Level of Evidence: Low

Recommendation: Conditional

Consensus Statements

12. Women with IBD who are pregnant and with active disease should start or optimize the same appropriate therapies as in nonpregnant patients, except for thiopurines, methotrexate, janus kinase inhibitors and sphingosine 1 receptor modulators.

13. In women with IBD who continue thiopurines during pregnancy, precaution should be taken for intrahepatic cholestasis by measurement of liver enzymes, metabolite levels and consideration of split dosing.

14. Women with IBD who are pregnant and have infections, fistula or pouchitis that require antibiotics may take an appropriate course of a low-risk antibiotic.

Consensus Statements

15. Women with IBD may initiate or continue calcineurin inhibitors (cyclosporine and tacrolimus) during pregnancy with careful monitoring if there are no viable alternate treatment options available.

16. Women with IBD who are pregnant or attempting conception should continue biosimilars to existing biologics.

17. Women with IBD who are pregnant or attempting conception should continue anti-interleukin-23 therapy throughout pregnancy (mirikizumab, risankizumab, guselkumab).

Consensus Statements

Women with IBD should discontinue:

18. Ozanimod (at least 3 months)
19. Etrasimod (at least 1-2 weeks)
20. Tofacitinib (at least 4 weeks)
21. Upadacitinib (at least 4 weeks)
22. Filgotinib (at least 4 weeks)

...prior to conception unless there is no effective alternative therapy to maintain maternal health

Consensus Statement 13: Thiopurines

Recent FDA announcement, 29 April 2024
"Rare risk of intrahepatic cholestasis of pregnancy"

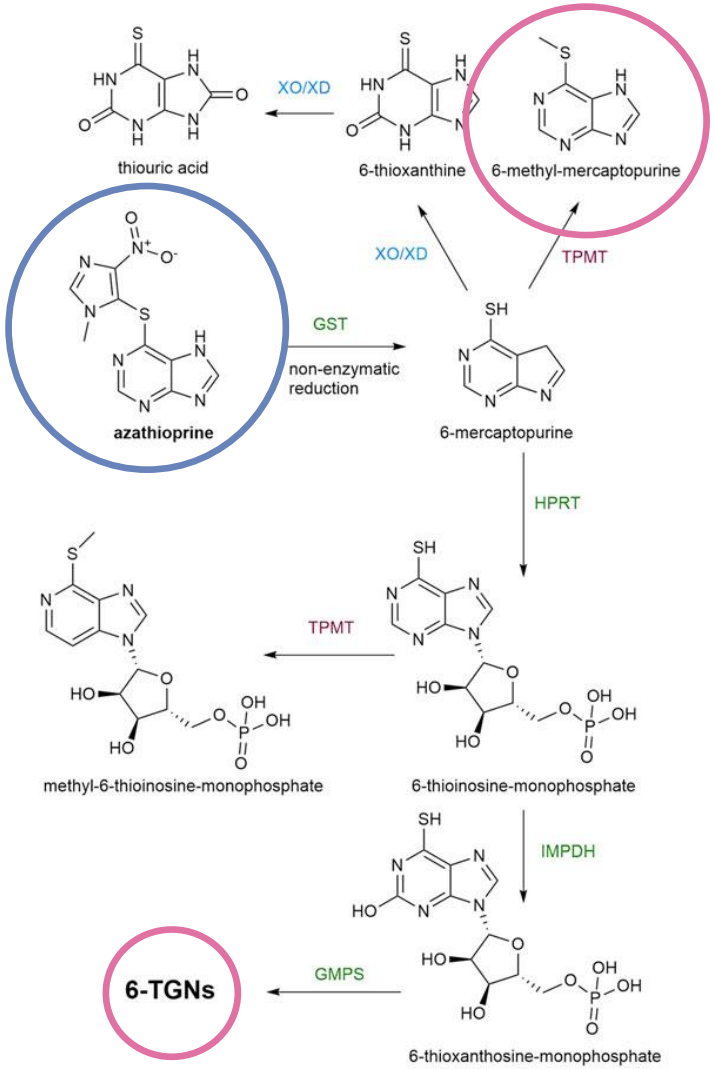
Incidence of 1.1% in the general population

IBD data: Prentice 2024, Selinger 2023, Kanis 2021

Practical considerations

Split dosing of thiopurine; Allopurinol co-therapy has limited safety data; Use of thioguanine; or Biologic monotherapy

Shunting to the 6-MMP pathway



MMP:TGN increases over pregnancy

Jharap 2014, Flanagan 2021

IBD Medications from Pre-conception through Pregnancy

Medication	Pre-conception	1st Trimester	2nd Trimester	3rd Trimester
Aminosalicylates • Folic acid supplementation with Sulfasalazine	✓	✓	✓	✓
Thiopurine	✓	✓	✓	✓
Methotrexate • Teratogen: • Cessation 1-3 months prior to conception	✗	✗	✗	✗
Corticosteroids • Minimize use • Employ steroid sparing therapy	✓	✓	✓	✓

IBD Medications from Pre-conception through Pregnancy and Lactation

Medication	Pre-conception	1st Trimester	2nd Trimester	3rd Trimester
Anti-Tumor Necrosis	✓	✓	✓	✓
Anti-Integrin	✓	✓	✓	✓
Anti IL-12/23 or Anti IL-23	✓	✓	✓	✓
JAK Inhibitors • Avoid • Use only if no other viable option for maternal health	!	!	!	!

Risankizumab Placental Transfer

Serum Concentration (mcg/ml)			
Patient	1	2	3
Second Trimester Trough	20.10		
Mother	28.60	9.48	12.11
Umbilical Cord Blood	5.96	3.19	4.14
Infant	6.53	3.12	--
Ratio Infant/Cord: Mother	0.23	0.33	0.34

Mahadevan et al Inflamm Bowel Disease 2024

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

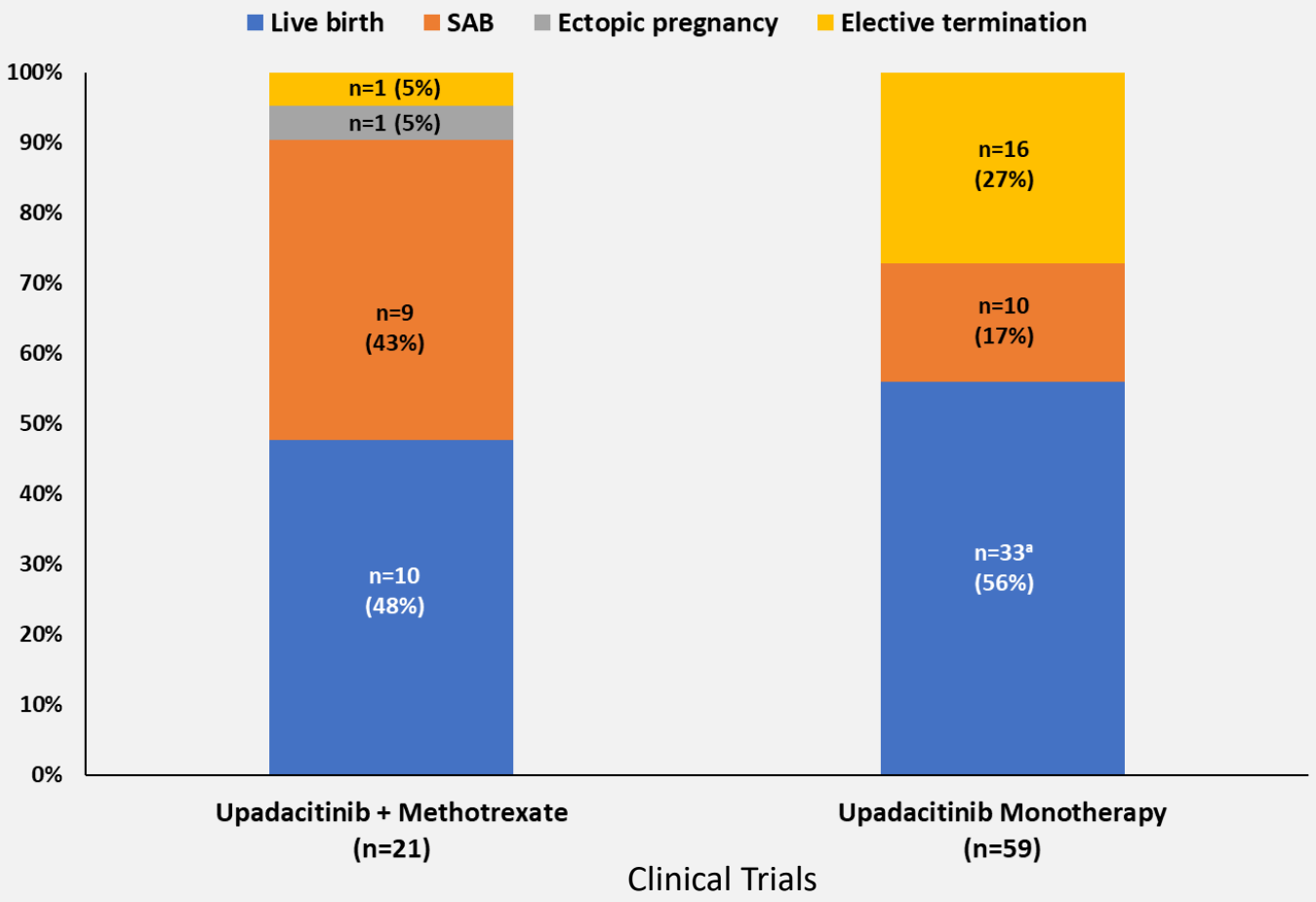
(included 2 cases from the same patient)

[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

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



Animal Reprotoxicity Data

- 1.6x, 15x [15 mg QD]
- **<u>0.8x, 7.6x [30 mg QD]</u>**
- 0.6x, 5.6x [45 mg QD]

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%)
  - Elective terminations (15%)
  - Ectopic pregnancy (2%)

Mahadevan et al Drug Saf. 2024

Maternal factors impacting pregnancy

Fertility

Pre-conception counseling and optimization

Management of disease activity during pregnancy

Management of pregnancy

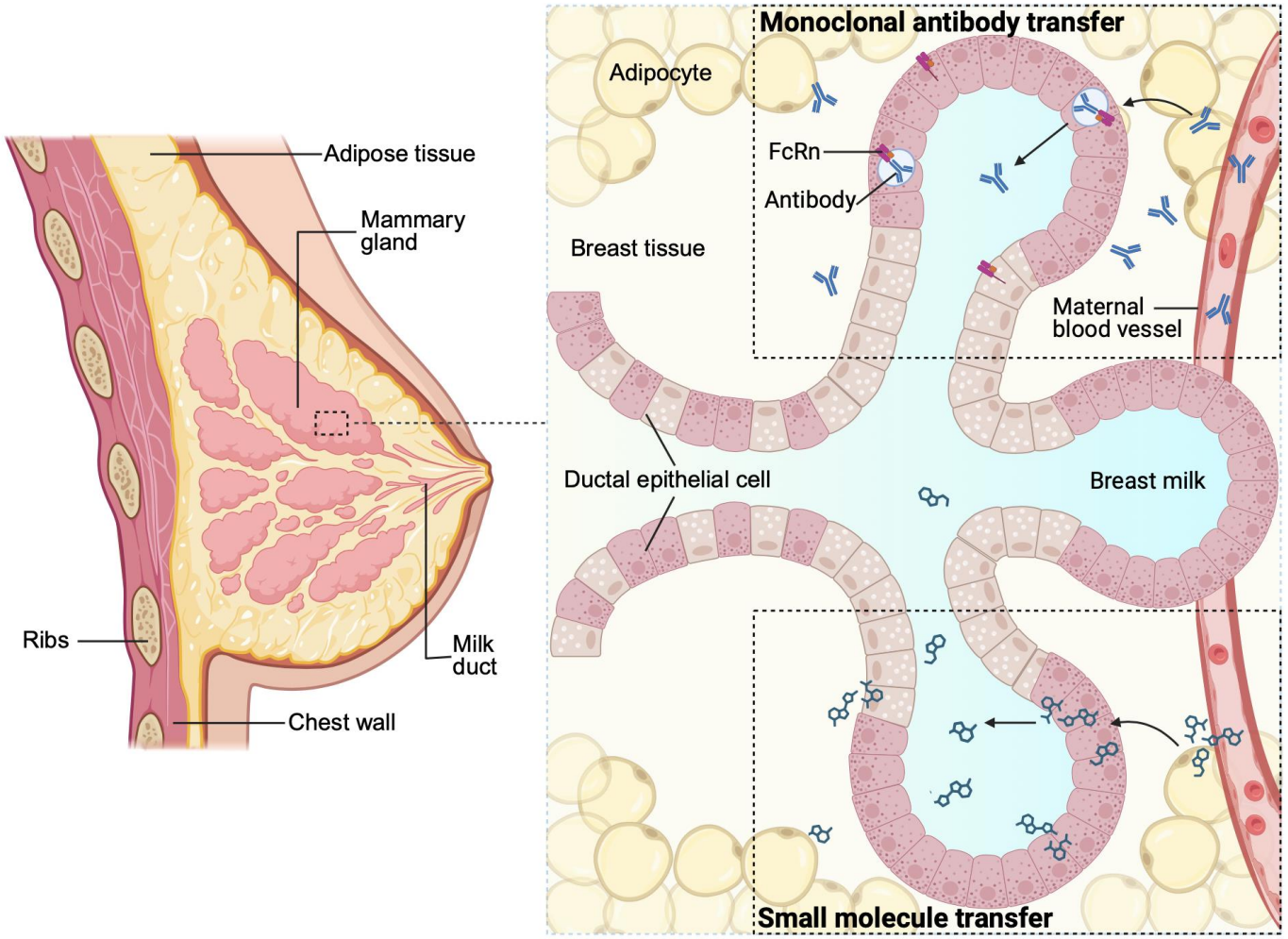
IBD medications during pregnancy

IBD medications during lactation

Pregnancy adverse events

Fetal and neonatal adverse events

Vaccines



The transfer of monoclonal antibodies and small molecules

from the maternal blood into breast milk during lactation.

Monoclonal antibodies (mAbs) & breastfeeding

The estimated infant mAb exposure via breastmilk (Relative Infant Dose)

For most drugs, a weight-adjusted percentage of the maternal dosage (Relative Infant Dose) of ≤ 10% is considered relatively safe.[1,2]

In infants exposed *in utero* to *infliximab, adalimumab, vedolizumab* or *ustekinumab*, maternal breastfeeding did **not** affect neonatal clearance of the drug.[4-6]

1.LaHue SC et al. Neurol Neuroimmunol Neuroinflamm 2020 , 2.Sah BNP et al. Front Nutr. 2020,
3.Krysko KM et al. Lancet Neurol 2023, 4.Julsgaard M et al. Gastroenterology 2016,
5.Julsgaard M et al. AP&T 2021, 6.Julsgaard M et al. Clin Gas Hep 2024.

GRADE Statement 21:

We recommend breastfeeding as it is NOT associated with an increased risk of disease exacerbation in women with IBD.

Level of Evidence:

Very low

Recommendation:

Strong

GRADE Statement 22:

We suggest counseling that infants born to mothers on anti-tumor necrosis factor therapy who breastfeed have no increased risk of infection in the first 12 months of life.

Level of Evidence:

Very low

Recommendation:

Conditional

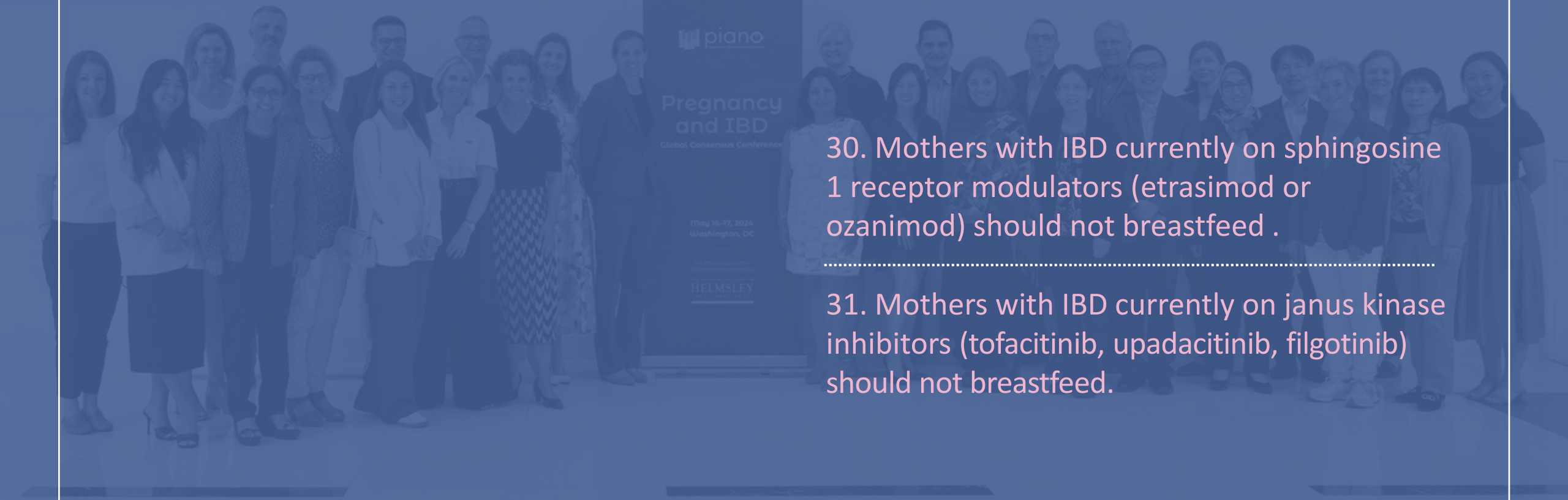
Consensus Statements

Mothers with IBD currently on:

23. 5-aminosalicylates/sulfasalazine
24. Thiopurines
25. Corticosteroids
26. Anti-tumor necrosis factor agents (Infliximab, adalimumab, golimumab, certolizumab)
27. Anti-integrins (vedolizumab, natalizumab)
28. Anti-interleukin-12/23 and anti-interluekin-23 (ustekinumab, risankizumab, mirikizumab, guselkumab).
29. Biosimilars

…may breastfeed

Consensus Statements



30. Mothers with IBD currently on sphingosine 1 receptor modulators (etrasimod or ozanimod) should not breastfeed .

31. Mothers with IBD currently on janus kinase inhibitors (tofacitinib, upadacitinib, filgotinib) should not breastfeed.

Safe to Breastfeed On

- 5-ASAs
- Sulfasalazine
- Thiopurines
- Corticosteroids
- Anti-TNFs
- Anti-integrins
- Anti-IL-23s
- Biosimilars

Avoid Breastfeeding On

- S1Ps
- JAK inhibitors
- Methotrexate

JAK-inhibitors & breastfeeding

Tofacitinib

- Detectable in breastmilk of 2 lactating women
  - 5 and 10 mg BID, respectively[1,2]
- "Worst-case": **Relative Infant Dose 3.4%**[1,2]
- 3 infants exposed to tofacitinib during pregnancy/breastfeeding → normal development[2,3]
  - 1 infant: normal immunological assessment at 3 months of life. [3]

Upadacitinib & filgotinib

- No available human lactation data
- **EMA & FDA** recommend **avoidance of breastfeeding**.[4,5]

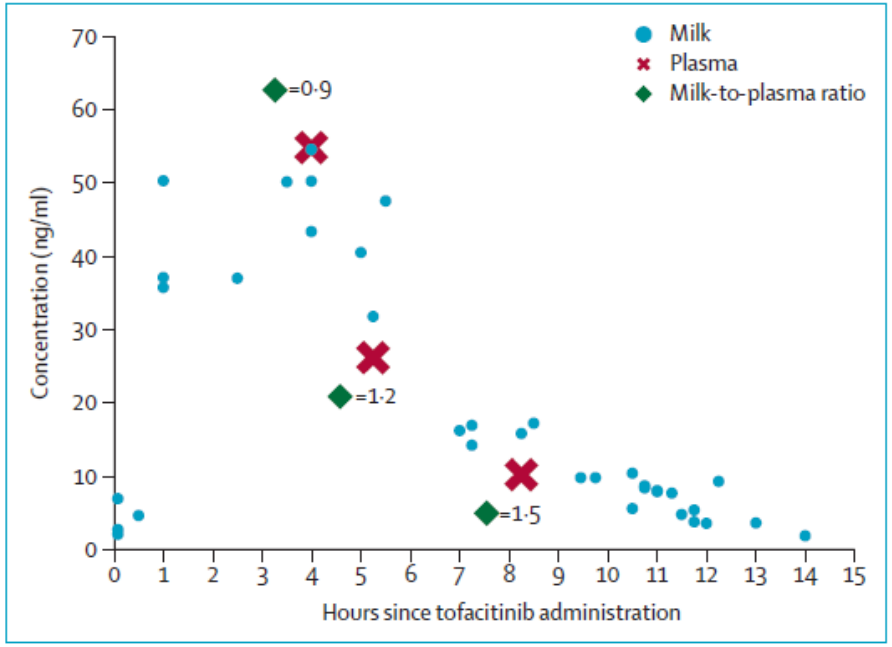


Figure: **Tofacitinib concentrations in maternal milk and plasma**
37 milk samples collected on 25 individual days during a 63-day period. **Ref. 1**

Recommendation

Due to no/limited human safety data including unknown effects on the immune system of the suckling infant, breastfeeding should be avoided in case of treatment with a JAK-inhibitor

1. Julsgaard M et. al. Lancet Gas Hep 2023, 2. Mitrova K et. al. Clin Gas Hep 2024,
3. Ernest-Suarez K et. al. Inflamm Bowel Dis 2024. 4. www.ema.europa.eu 5. www.accessdata.fda.gov

Maternal factors impacting pregnancy

Fertility

Pre-conception counseling and optimization

Management of disease activity during pregnancy

Management of pregnancy

IBD medications during pregnancy

IBD medications during lactation

Pregnancy adverse events

Fetal and neonatal adverse events

Vaccines

GRADE Statement 23:

We suggest counseling that women with IBD as compared to women without IBD have an increased risk of adverse pregnancy outcomes including low birth weight and preterm delivery.

Level of Evidence: Very low

Recommendation: Conditional

GRADE Statement 24:

We suggest counseling that women with IBD with moderate to severe disease activity have an increased risk of spontaneous abortion as compared to women without IBD or women with mild IBD.

Level of Evidence: Very low

Recommendation: Conditional

GRADE Statement 25:

We suggest counseling that pregnant women with IBD have an increased risk of venous thromboembolism during pregnancy as compared to pregnant women without IBD.

Level of Evidence: Low

Recommendation: Conditional

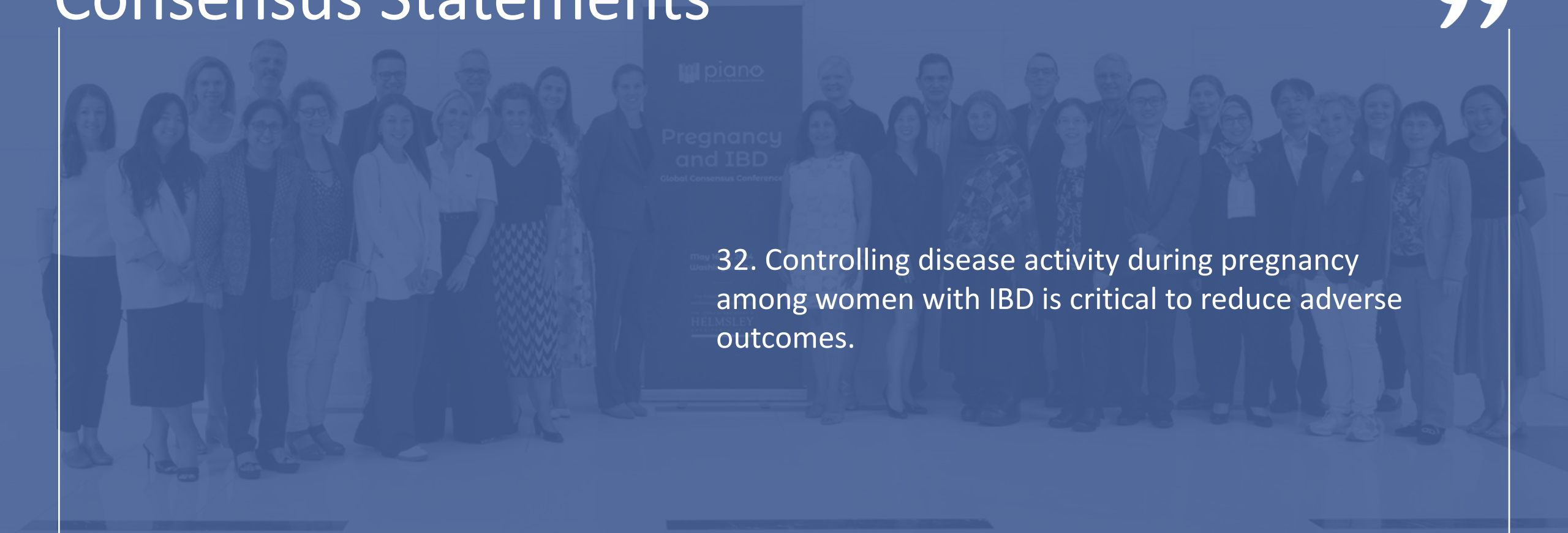
GRADE Statement 26:

We suggest counseling that pregnant women with IBD have an increased risk of venous thromboembolism during the postpartum as compared to pregnant women without IBD.

Level of Evidence: Low

Recommendation: Conditional

Consensus Statements



32. Controlling disease activity during pregnancy among women with IBD is critical to reduce adverse outcomes.

Maternal factors impacting pregnancy

Fertility

Pre-conception counseling and optimization

Management of disease activity during pregnancy

Management of pregnancy

IBD medications during pregnancy

IBD medications during lactation

Pregnancy adverse events

Fetal and neonatal adverse events

Vaccines

GRADE Statement 27:

We suggest counseling that children born to women with IBD have an increased rate of neonatal ICU admissions and hospitalizations in the first year of life compared to children born to women without IBD.

Level of Evidence:

Very Low

Recommendation:

Conditional

GRADE Statement 28:

We suggest counseling that children born to women with active IBD have an increased rate of small for gestational age and low birth weight compared to children born to women with inactive IBD .

Level of Evidence:

Very low

Recommendation:

Conditional

GRADE Statement 29:

We suggest counseling that children born to women treated with anti-tumor necrosis factor therapy, ustekinumab or vedolizumab during pregnancy have no increased risk for early childhood malignancy.

Level of Evidence:

Very low

Recommendation:

Conditional

GRADE Statement 30:

We suggest counseling that children born to women treated with anti-tumor necrosis factor therapy, ustekinumab or vedolizumab during pregnancy have no increased risk for early childhood developmental delay.

Level of Evidence:

Very low

Recommendation:

Conditional

GRADE Statement 31:

We suggest counseling that children born to women treated with thiopurine therapy during pregnancy have no increased risk for early childhood developmental delay.

Level of Evidence:

Very low

Recommendation:

Conditional

Pregnancy and Neonatal Adverse Events

Increased risk of low birth weight with active maternal IBD

Increased risk of Neonatal intensive care unit

Increased risk of small for gestational age with active maternal IBD

Increased risk of pre-term delivery

Increased risk of spontaneous abortion with active disease

Increased risk of venous thromboembolism

Maternal factors impacting pregnancy

Fertility

Pre-conception counseling and optimization

Management of disease activity during pregnancy

Management of pregnancy

IBD medications during pregnancy

IBD medications during lactation

Pregnancy adverse events

Fetal and neonatal adverse events

Vaccines

GRADE Statement 32:

We recommend that inactive vaccines be provided to children born to mothers with IBD on anti-tumor necrosis factor agents.

Level of Evidence:

Very Low

Recommendation:

Strong

GRADE Statement 33:

We suggest that live rotavirus vaccine may be provided in children with in-utero exposure to biologics.

Level of Evidence:

Very low

Recommendation:

Conditional

GRADE Statement 34:

We recommend that live Bacillus Calmette-Guérin vaccine be avoided in the first 6 months* of life in children with in-utero exposure to anti-tumor necrosis factor therapy due to risk of disseminated tuberculosis and associated mortality.

*Regional risk should be considered

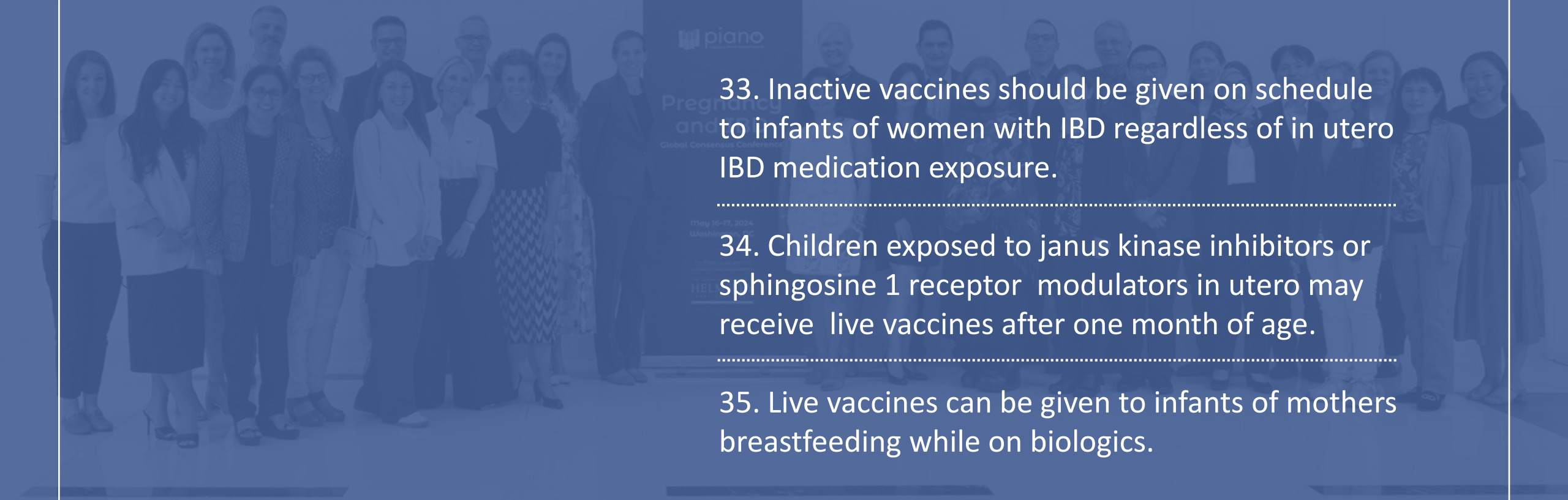
Level of Evidence:

Very low

Recommendation:

Strong

Consensus Statements



33. Inactive vaccines should be given on schedule to infants of women with IBD regardless of in utero IBD medication exposure.

34. Children exposed to janus kinase inhibitors or sphingosine 1 receptor modulators in utero may receive live vaccines after one month of age.

35. Live vaccines can be given to infants of mothers breastfeeding while on biologics.

Live attenuated Rotavirus vaccine

Infants exposed *in utero* to anti-TNF

309 infants → **live attenuated Rotavirus vaccine** → **no serious adverse events**.[1-5]

Systematic review and meta-analysis: **low risk of minor adverse event** (fever/diarrhea) (6/46, 15%).[3]

Canadian Immunization Research Network:[4]

- IFX (67/191 [35%]), ADA (49 [26%]), UST (18 [9%]), VDZ (17 [9%])

191 exposed
178 (93%) in T3

187 recommend to vax

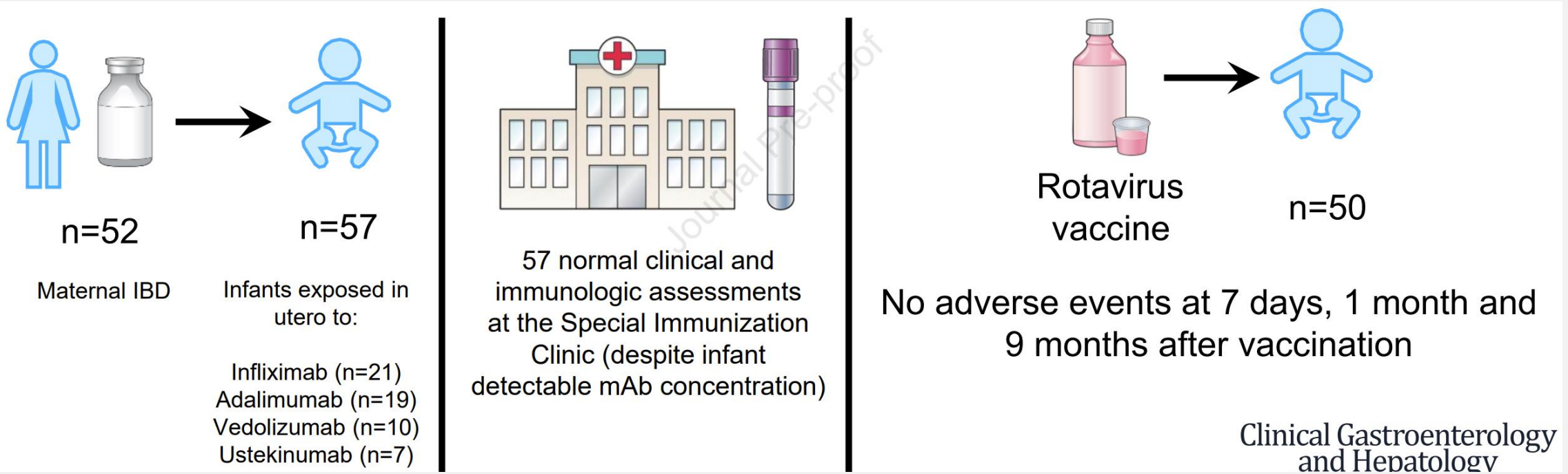
168 initiated rotavirus vaccine

No serious adverse reactions

1. Chaparro et al. J Crohns Colitis. 2023, 2. Benchimol et al. J Can Assoc Gastroenterol. 2021,
3. Goulden et al. Rheumatology (Oxford). 2022;
4. Fitzpatrick et al. Lancet Child Adolesc Health. 2023,
5. Gisbert et al. J Crohns Colitis. 2023

IBD Data: Safety Rotavirus Vaccine

Live Rotavirus Vaccination Appears Low-risk in Infants Born to Mothers with IBD on Biologics



Ernest Suarez et al. Clin Gastroenterol Hepatol. 2024 Jul 30

Summary

Key Points:

Reduced fertility with active disease and IPAA

No risk of flare with oocyte retrieval

Increased risk of pre-term delivery

Increased risk of spontaneous abortion with active disease

Increased risk of VTE

Clinical Guidance:

- Continue all biologics and thiopurines throughout pregnancy and lactation
- Avoid small molecules with pregnancy and lactation
- Provide preconception counseling to improve outcomes
- Provide low dose aspirin to reduce pre-term preeclampsia
- Perform a cesarean section for delivery if active perianal fistula, rectovaginal fistula, IPAA

Summary

Key Points:

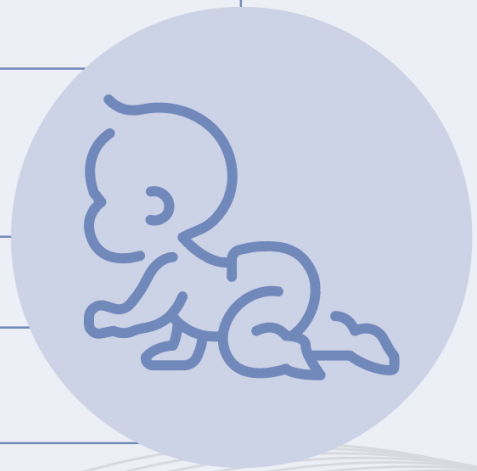
Increased risk of IBD if first degree relative with IBD

Increased risk of low birth weight with active maternal IBD

Increased risk of NICU

Increased risk of SGA with active maternal IBD

No increased risk of infant infections, malignancy, or developmental delay with biologic exposure



Clinical Guidance:

- Inactive vaccines should be given on schedule regardless of medication exposure
- Live vaccines should be given on schedule EXCEPT BCG, which can be given after six months in infants exposed to biologics in utero

piano
Pregnancy in IBD And Neonatal Outcomes

Questions?

To enroll in the PIANO registry for US residents: pianostudy.org

Slide Decks (English/Spanish)
Patient Videos (7 languages)
AIBDN Videos