INSELGRUPPE

IBD – Fertility, Pregnancy and Lactation

Wednesday Seminar 4.9.2024

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What will be covered?

European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation

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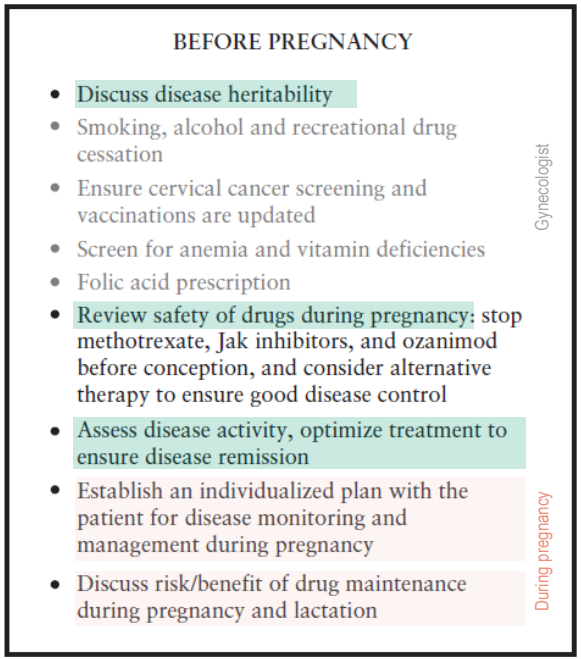
1. How should we counsel IBD patients with pregnancy desire?
2. How does IBD affect fertility?
3. How to manage IBD during pregnancy?
4. How to manage therapy after delivery?

How should we counsel before pregnancy?



What do you tell patients who ask about IBD heritability?

Counseling – IBD Heritability I

Table 3. Prevalence of Ulcerative Colitis and Crohn's Disease per 100,000 Persons among First- and Second-Degree Relatives.*

Disease in Proband	Prevalence among First-Degree Relatives		Prevalence among Second-Degree Relatives	
	Ulcerative colitis	Crohn's disease	Ulcerative colitis	Crohn's disease
Ulcerative colitis	1522 (1114, 2030)	99 (21, 288)	264 (165, 542)	12 (0, 67)
Crohn's disease	711 (230, 1660)	569 (155, 1457)	52 (1, 289)	156 (32, 455)

Conclusions. The 10-fold increase in the familial risk of ulcerative colitis and Crohn's disease strongly suggests that these disorders have a genetic cause.

Orholm M et al. N Engl J Med 1991; 324:84-88.

Counseling – IBD Heritability II

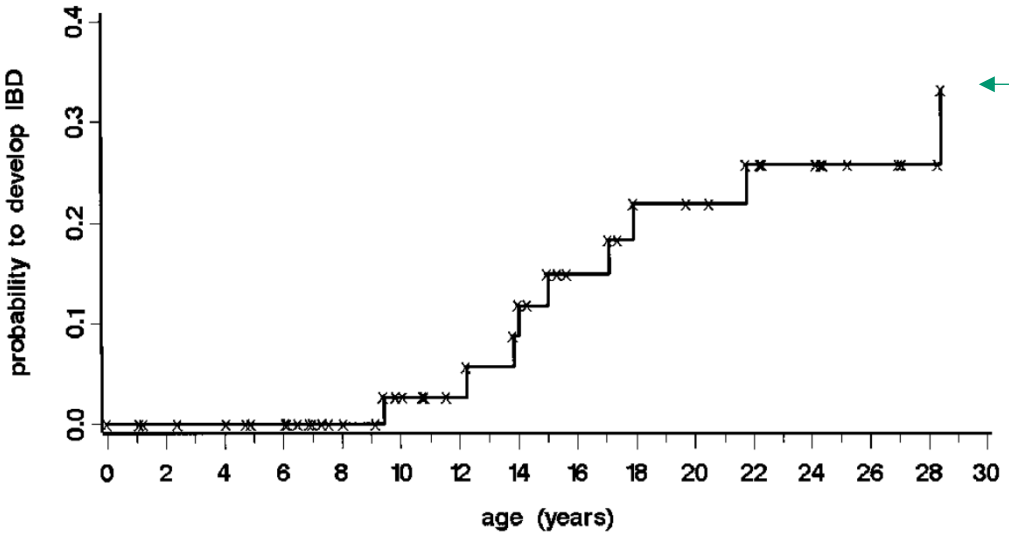
Concordance for inflammatory bowel disease in twin pairs

	Identical twin		Non-identical twin	
Proband's diagnosis	**Disease**	**No disease**	**Disease**	**No disease**
Crohn's disease	5	20	3	43
Ulcerative colitis	6	32	1	33
Total	11	52	4	76

- Significantly more IBD cases in identical vs. non-identical twins of IBD patients
- But: absolute risk only 17% (other factors)

Thompson NP et al. BMJ. 1996;312(7023):95-6.

Counseling – IBD Heritability III



33% life-time risk of CD if both parents have CD

Laharie D et al. Gastroenterology. 2001;120(4):816-9

Counseling – IBD Heritability IV

- Risk of **CD** in FDRs of **CD** patients is **8-fold** increased
- Risk of **UC** in FDRs of **UC** patients if **4-fold** increased

- But: overall risk is still relatively low if **one parent** is affected (**max. 3–5%** vs. 0.5–1% in the general population)

Statement 3

Paternal or maternal IBD increases the risk of IBD development for the offspring [EL3]. The risk is greater for CD and is much greater when both parents are affected [EL3]

Counseling – Safety of drugs during pregnancy?

Table 1. ECCO overview of risks of drugs during pregnancy and lactation.

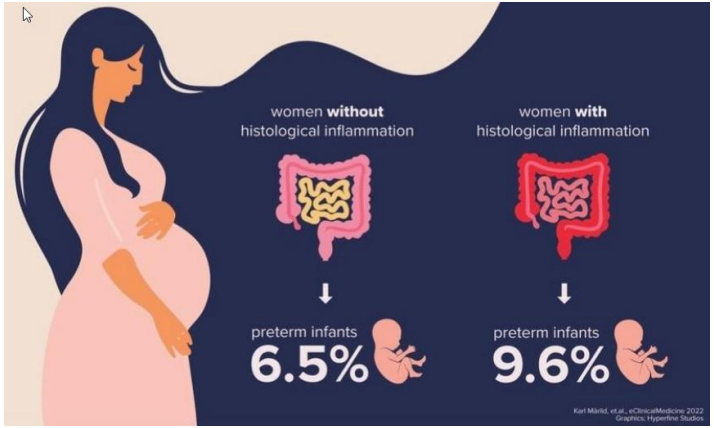
Drug	During pregnancy
Mesalazine	Low risk
Sulphasalazine	Low risk
Corticosteroids	Low risk
Metronidazole	Low risk*
Ciprofloxacin	Avoid in T1*
Thiopurines	Low risk
Thiopurines + allopurinol	Limited data
Ciclosporin Tacrolimus	Low risk, limited data
Anti-TNF	Low risk
Vedolizumab	Low risk, limited data
Ustekinumab	Low risk, limited data
Methotrexate	Contraindicated
Thalidomide	Contraindicated
Tofacitinib	Contraindicated
Filgotinib	Contraindicated
Ozanimod	Contraindicated

All biologics and thiopurines are safe

!

Counseling – Timing of pregnancy?

- IBD patients who conceive when their disease is active are more likely to have active disease during pregnancy[1]
- IBD activity during pregnancy is associated with stillbirth, preterm birth, SGA, low birthweight[2]
- Quiescent IBD: no increase in adverse pregnancy outcomes



Goal: 3 months of steroid-free remission on stable therapy prior to conceiving

1 Abhyankar A et al. Aliment Pharmacol Ther. 2013;38(5):460-6
2 Nielsen OH et al. Lancet. 2024;403(10433):1291-1303
Mårild K et al. EClinicalMedicine. 2022;53:101722

Fertility in IBD?

Statement 6

Active disease is associated with decreased fertility in women with IBD [EL3]. Achieving clinical remission may increase the probabilityof successful conception. Active disease is also associated with decreased fertility in men with IBD [EL4]

Statement 7

Most of the commonly used IBD drugs have no demonstrated impact on fertility, in particular sperm quality [EL4]. Sulphasalazine is associated with reversible oligospermia

Fertility in IBD – (pouch) surgery reduces fertility

Table 3.
Fertility Before and After RPC[a]

Study (yr)	No. of Females	No. of Females Infertile Before RPC	Incidence of Fertility Treatment Before RPC	No. of Females Infertile After RPC	Incidence of Fertility Treatment After RPC
Bambrick *et al.*[14] 1996	92	0	–	9 (8)	–
Counihan *et al.*[9] 1994	203	2 (5)	–	9 (18)	–
Gorgun *et al.*[10] 2004*	135	38 (48)	42	56 (76)	51
Ording Olsen *et al.*[27] 2002*	290	–	6	–	11
Oresland *et al.*[28] 1994*	21	–	–	62 (13)	–
Tiainen *et al.*[32] 1999*	51	10 (5)	–	20 (10)	–
Total	945	12 (78)	–	26 (167)	–
Total of higher quality studies*	650	17 (61)	–	43 (154)	–

RPC = restorative proctocolectomy; * = high quality studies.
Data are percentages with numbers in parentheses unless otherwise indicated.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of women/pregnancies (studies)	Certainty of the evidence (GRADE)
	Risk with no previous surgery	Risk with any previous IBD surgery			
Infertilty at 12 months	Study population		RR 5.45 (0.41 to 72.57)	114 women (2 observational studies)	⊕⊝⊝⊝ Very low[a,b]
	47 per 1000	253 per 1000 (19 to 1000)			
Infertility at 24 months	Study population		RR 3.59 (1.32 to 9.73)	106 women (1 observational study)	⊕⊝⊝⊝ Very low[a,b]
	83 per 1000	297 per 1000 (109 to 805)			

Cornish JA et al. Dis Colon Rectum. 2007;50(8):1128-38
Lee S et al. Cochrane Database Syst Rev. 2019;7(7):CD012711

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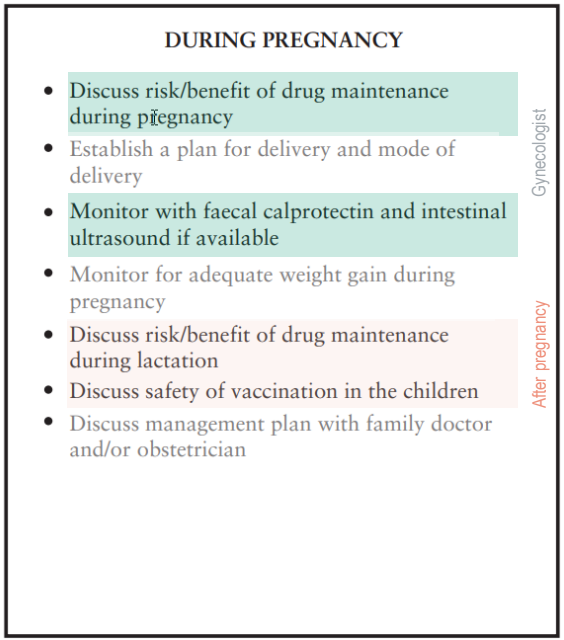
Management of IBD during pregnancy

Management during pregnancy – overview



Impact of pregnancy on IBD course

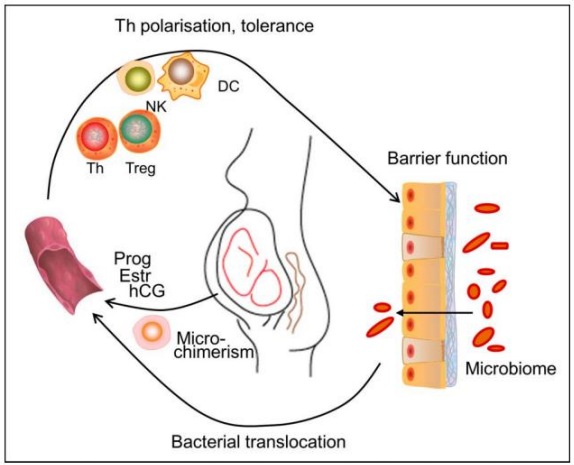


Figure 1. Interaction between physiological changes during pregnancy and the pathophysiology of inflammatory bowel disease.

Numerous modulatory effects of pregnancy on IBD

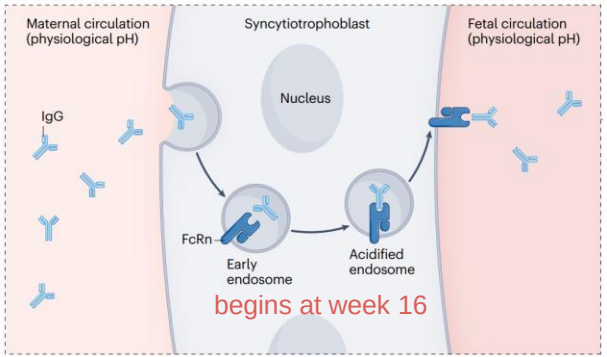
- Changes in the microbiome
- Barrier integrity ↑
- Changes in innate/adaptive immune system
- Microchimerism

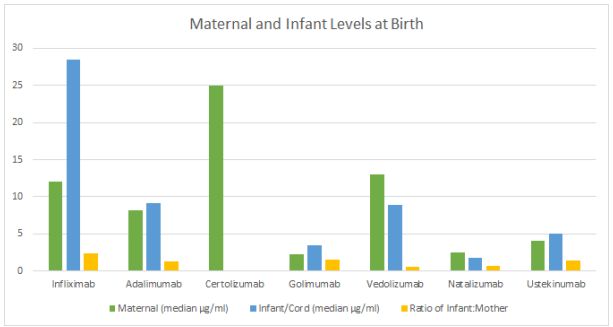
Statement 10

Pregnancy may increase the risk of relapse or worsening disease in patients with UC and complications in patients with CD, specially if disease is active at conception [EL3]. IBD remission before conception is recommended [EL2]

van der Giessen J et al. Clin Transl Gastroenterol. 2019;10(3):e00009.

Risk/benefit of drug maintenance during pregnancy





- 5-ASA, thiopurines and monoclonal antibodies can cross the maternal–fetal interface and have potential effects on the fetus
- But: flares → adverse pregnancy outcomes
- *In utero* exposure to anti-TNF is not associated with increased short-term or long-term risk of severe infections in children (TEDDY study[1] and PIANO trial[2])
- No evidence of adverse maternal or fetal events for non-TNF biologics

Chaparro M et al. Am J Gastroenterol. 2018;113(3):396-403 (TEDDY)
Mahadevan U et al. Gastroenterology. 2021;160(4):1131-1139 (PIANO)
Brondfield MN et al. Nat Rev Gastroenterol Hepatol. 2023;20(8):504-523

Drug maintenance during pregnancy?

Statement 19

For women with active disease just before or during pregnancy, or with disease that is difficult to control, continuation of anti-TNF [EL3] or non-TNF biologics [EL5] throughout pregnancy is recommended. The last dose of anti-TNF in the third trimester should be timed in accordance with the presumed due date to reduce foetal exposure [EL5]

If non-complicated case **and**
long-term remission:
Discontinuation of anti-TNF in the 3rd trimester possible
(but not recommended)

How to monitor during pregnancy?

Do

- Fecal Calprotectin
- Intestinal ultrasound
- MRI w/o contrast
- Endoscopy if needed

Avoid

- CT scan
- Video capsule endoscopy

How to deal with flares during pregnancy?

Statement 15

Pregnant women experiencing a flare should be managed according to current guidelines for non-pregnant patients, with 5-ASA, steroids, ciclosporin, anti-TNF agents [EL4], ustekinumab, or vedolizumab [EL5].
Initiating monotherapy with a thiopurine is generally not recommended due to the slow onset of action and the potential risk of adverse events [EL5]. Currently, JAK inhibitors and S1P receptor modulators should be avoided during pregnancy [EL5]

Statement 16

In case of a flare beyond gestational week 37, early delivery could be considered prior to initiation of medical therapy [EL5]

Statement 17

Indications for surgery in pregnant women with IBD are the same as for non-pregnant patients [EL5]. The indication for IBD-related surgery during pregnancy should be determined promptly, based on IBD severity and general maternal conditions. Urgent surgery should be performed if clinically indicated, regardless of the gestational age [EL5].
The surgical management should be discussed in a multidisciplinary team involving gastroenterologists, colorectal surgeons, obstetricians, and neonatal specialists, as required [EL5]

Proposed care pathway during pregnancy

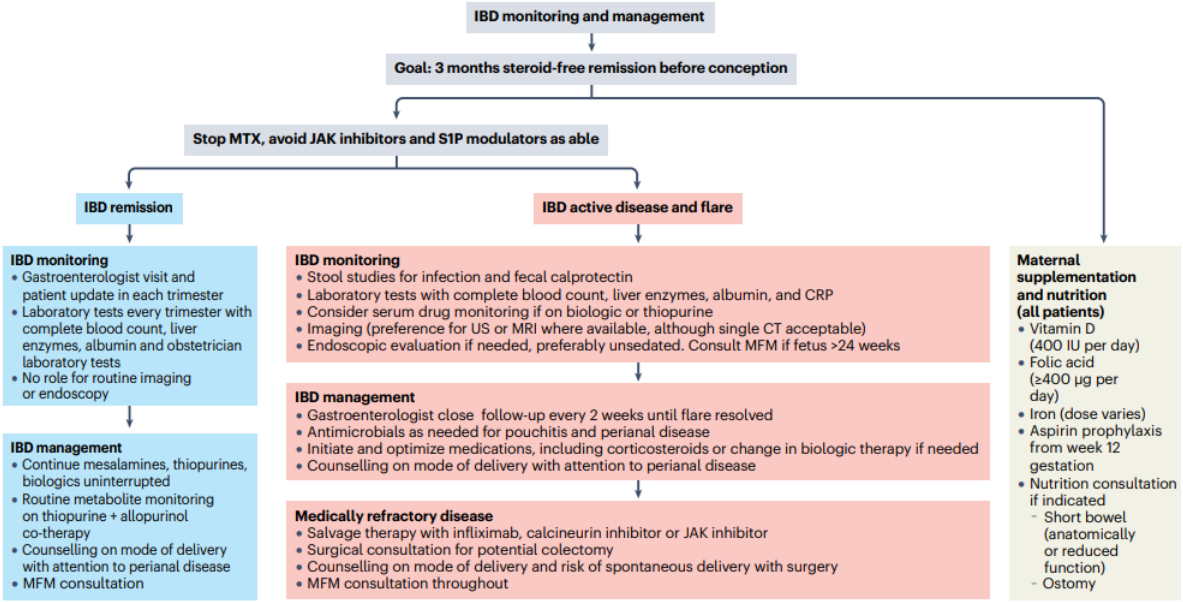


Fig. 3 | A proposed care pathway for monitoring and management of IBD during pregnancy. Key components of monitoring patients with IBD who begin pregnancy in remission or who experience flare of their disease, as well as management steps for quiescent or active disease. The care pathway also highlights supplementation and nutrition recommendations for all pregnant patients with IBD. CRP, C-reactive protein; IBD, inflammatory bowel disease; JAK, Janus kinase; MFM, maternal–fetal medicine; MTX, methotrexate; S1P, sphingosine 1-phosphate; US, ultrasonography.

Brondfield MN et al. Nat Rev Gastroenterol Hepatol. 2023;20(8):504-523

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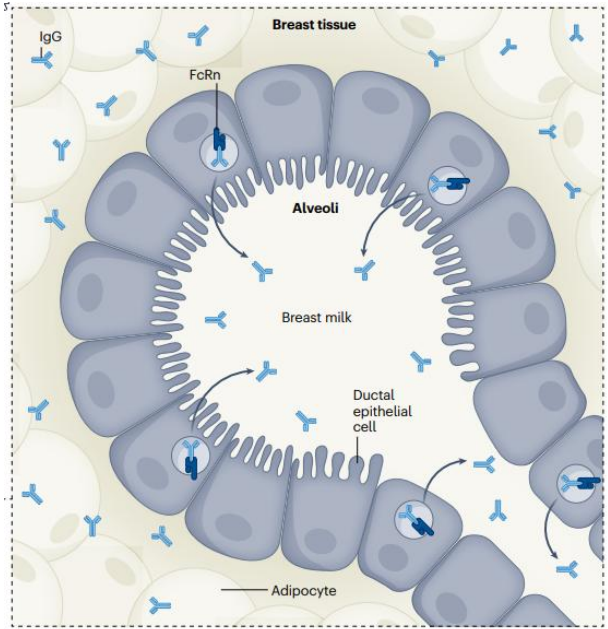
Management of IBD after delivery

Management after pregnancy – overview

AFTER DELIVERY

- Promptly restart treatment in women that stopped therapy during pregnancy
- Discuss safety of drugs during lactation
- Postpone live vaccines during the first 6–12 months of life in children exposed to biologics in utero, or until levels in children are undetectable
- Screen for mental health problems in the post-partum period

Safety of drugs during lactation



- Transfer of IgG immunoglobulins to breast milk occurs at minimal quantities
- No adverse outcomes have been reported in breastfed infants of mothers treated with biologics
- Breastfeeding does not influence disease activity

Drugs that are considered low-risk during pregnancy are also considered low-risk during breastfeeding and thus can be continued

Brondfield MN et al. Nat Rev Gastroenterol Hepatol. 2023;20(8):504-523

Safety of vaccinations in children of IBD patients

Statement 34

Inactivated vaccines are recommended according to national guidelines. In children exposed *in utero* to biologics, live attenuated vaccines should be withheld within the first year of life or until the biologic is no longer detectable in the infant's blood [EL3]

Interpretation: Findings from this study suggest that 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.

→ No relevant problem

	Säuglinge, Kinder und Jugendliche							
Alter *	Monate							
Impfung	Geburt	2	3**	4	5**	9	12***	12–18
DTP		DTP_a		DTP_a			DTP_a	
Polio		IPV		IPV			IPV	
Hib		Hib		Hib			Hib	✓ 4)
Hepatitis B	1)	HBV		HBV			HBV	
Pneumokokken		PCV		PCV			PCV	✓ 4)
Rotaviren		RV 2)		RV 2)				
Men. B			B		B			B 5)
Men. ACWY								ACWY 5)
MMR						MMR 3)	MMR 3)	✓ 6)
Varizellen						VZV	VZV	✓ 7)
HPV								
Herpes Zoster								
Influenza								

Fitzpatrick T et a. Lancet Child Adolesc Health. 2023 Sep;7(9):648-656

Summary

- Goal: >3 months steroid-free remission
- Discontinue MTX and modern small-molecule drugs (JAKi, ozanimod)
- All IBD biologics are safe during pregnancy and lactation
- Continue biologic therapy throughout pregnancy
- Monitor closely: fCal, IUS. Treat flares like in non-pregnant patients
- No relevant problems: lactation, vaccination of exposed children

Remission of IBD leads to good pregnancy outcomes

It’s a team effort