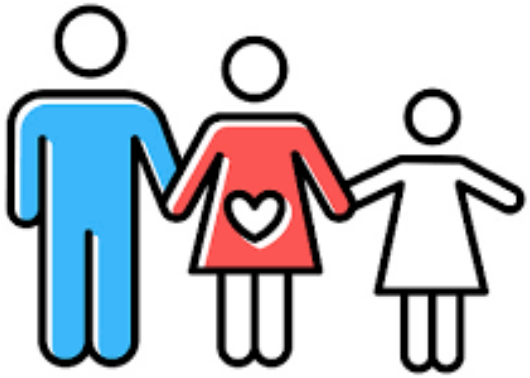
IBD and family planning



Marijn Visschedijk

19 maart 2024

MDL-arts

Leerdoelen

- Ziektebeloop tijdens zwangerschap
- Hoe behandel je een exacerbatie?
- Welke geneesmiddelen wel en niet?

Join by Web

PollEv.com/ibdandfamily

Join by Text

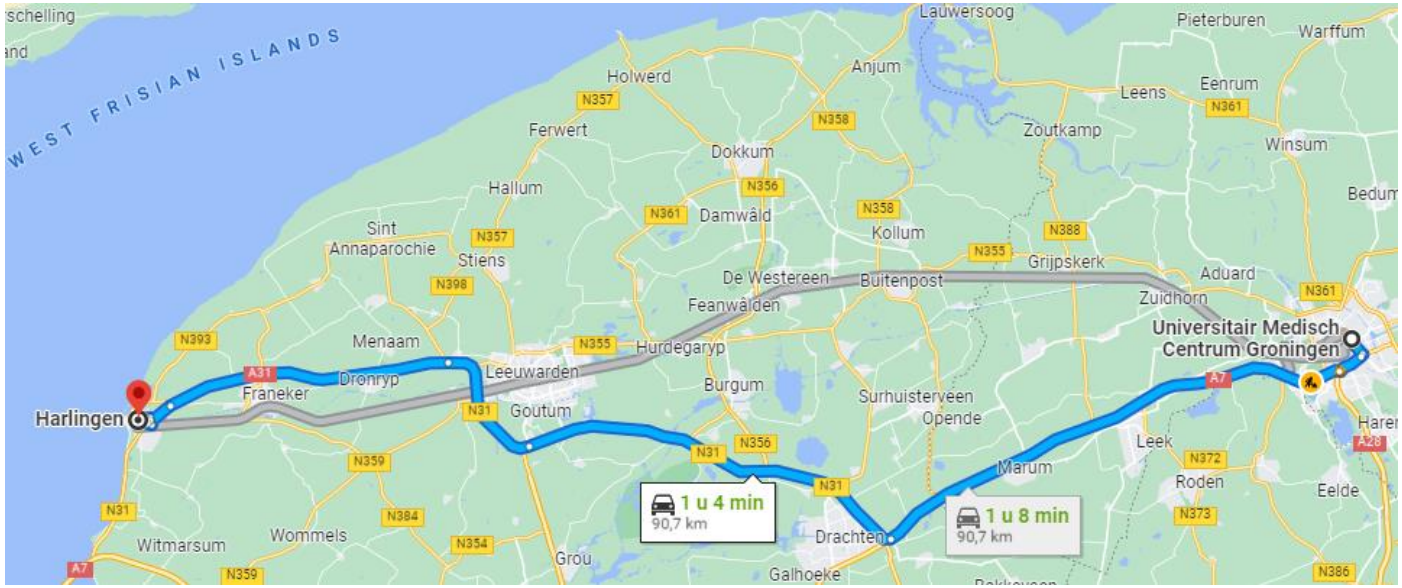
Send **ibdandfamily** and your message to **+31 970 0449 8375**

Skip for now, daarna Naam invoeren

How are you feeling today?

Case

- 27 years old lady, Polish origin, living in Harlingen (90km)



Case, first hospitalization

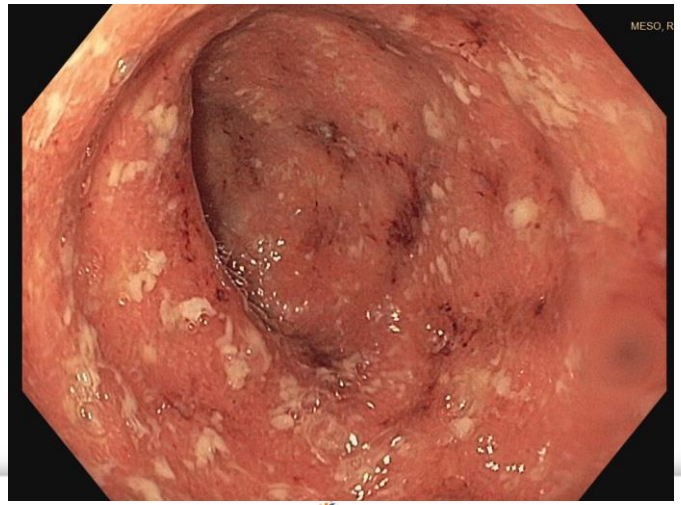
2-2022; consultation fertility-clinic because of primary subfertility

→ no abnormalities found. Advice: stop smoking

5-2022; hospitalized, 13 weeks pregnant; bloody diarrhoea and anaemia (Hb 3.6 mmol/L), CRP 30.

10-5-2022; pancolitis, endoscopic ulcerative colitis Mayo 3.

Calprotectine 1095 mg/kg



Wat is je beleid?

Nobody has responded yet.

Hang tight! Responses are coming in.

Case ~ treatment

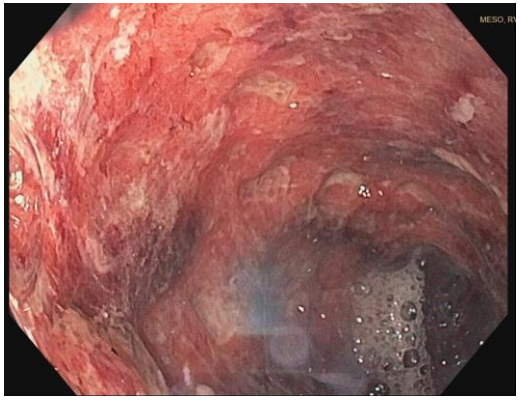
Prednisolon 40 mg/kg, non-respons

Start Cefuroxim/metrodinazole.

Start Infliximab 10 mg/kg.

Repeated 1 week later.

Start mesalazine



Sigmoidoscopy 14-5

19-6 re-hospitalisation, 18 weeks pregnancy, due to pancreatitis by mesalazine

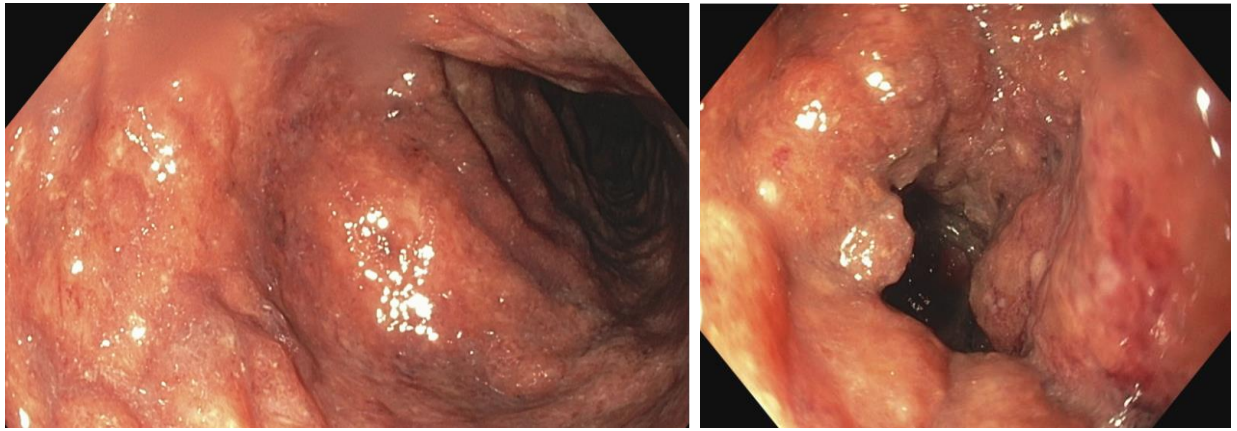
20-6 sigmoidoscopy, MAYO 2 pancolitis

→ Transfer to University Medical Hospital Groningen

Case ~ second hospitalisation

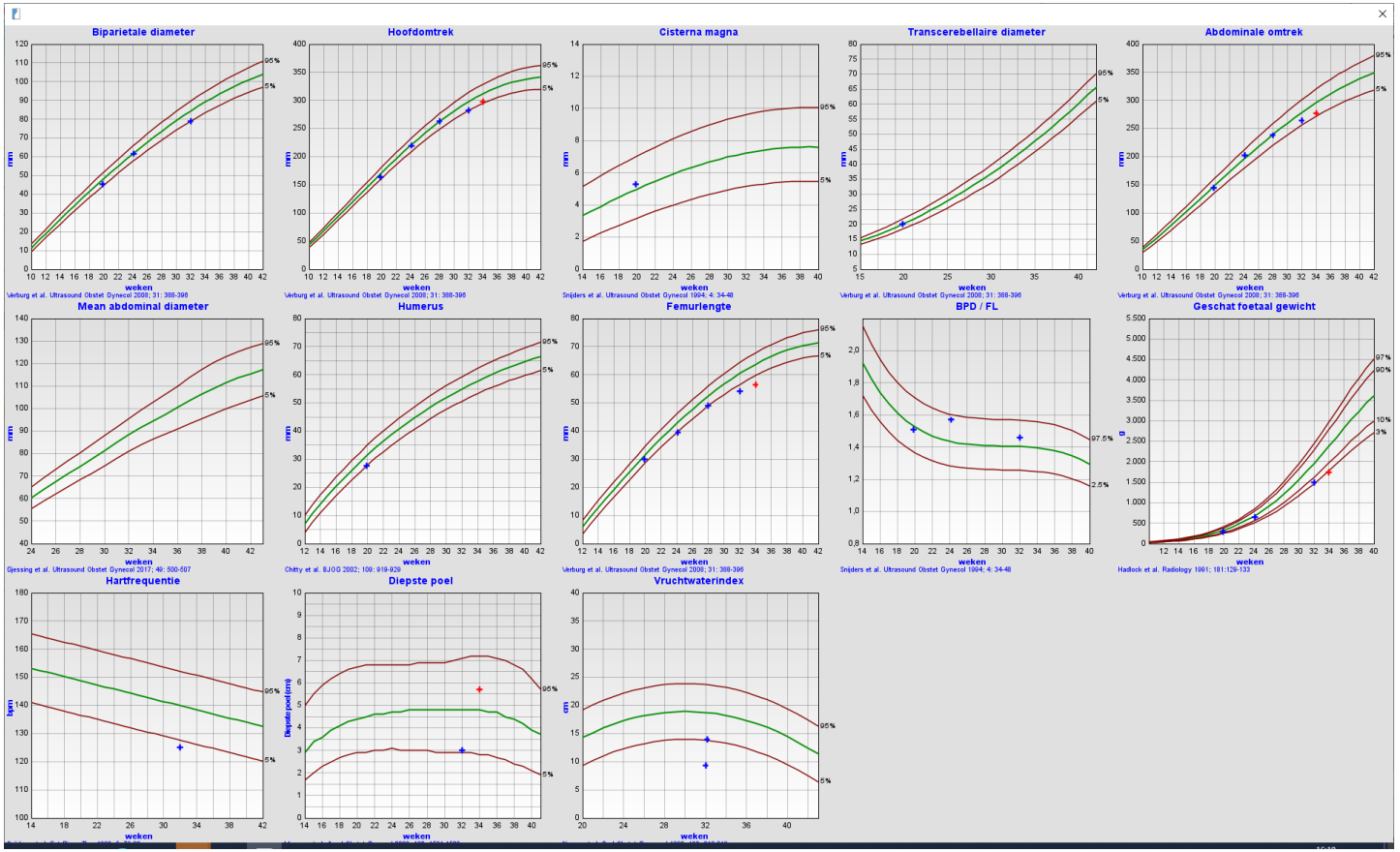
21-6 – 14-7 hospitalisation UMCG; mesalazine stop, fluid intravenous, prednisolon 2 times 30 mg,

CRP 54 → 1.1, normalising stool frequency.
IFX-level 25 ug/ml, top-level, Infliximab continued.



Sigmoidoscopy 23-6-2022

Outpatient clinic



AD 35w6D, hospitalisation abnormal CTG

Secundaire sectio caesarea; boy, birth weight 1840 g, normal apgar scores.

Active IBD
preconception

increased risk of IBD flare and associated adverse pregnancy outcomes

Active IBD
during pregnancy

increased risk of adverse pregnancy outcomes

The effect of IBD on pregnancy

IBD is associated with worse pregnancy outcomes

Adjusted OR	UC		CD	
	Stable disease	Flaring	Stable disease	Flaring
Preterm Birth	1.30 (0.89–1.90)	2.72 (2.12–3.48)	1.68 (1.12–2.52)	2.66 (1.89–3.74)
LBW	1.45 (0.98–2.14)	2.10 (1.51–2.90)	1.47 (0.89–2.43)	3.30 (2.29–4.74)
SGA	1.15 (0.68–1.92)	1.49 (0.96–2.31)	1.55 (0.87–2.75)	2.75 (1.72–4.38)
Still birth	1.18 (0.29–4.73)	0.57 (0.08–4.06)	3.06 (1.00–9.49)	4.48 (1.67–11.9)

470,110 singleton births in Sweden compared to 1833 to women with UC and 1220 to women with CD
Odds ratios with adjustments (aOR) for maternal age, parity, smoking status, body mass index, and comorbidity

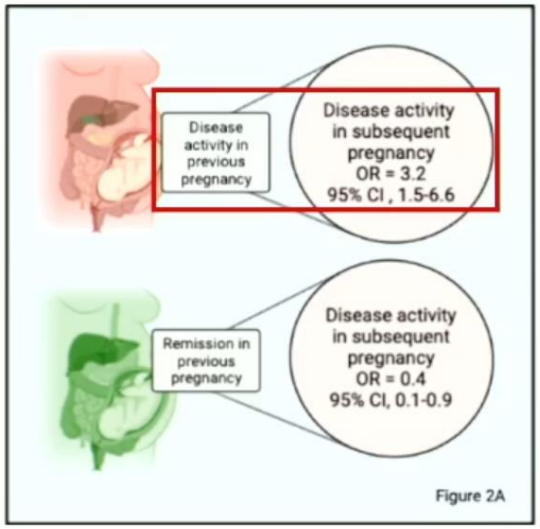
Disease activity during pregnancy →

2-5x ↑ risk of adverse pregnancy outcome (miscarriage, preterm birth, low birth weight, stillbirth)

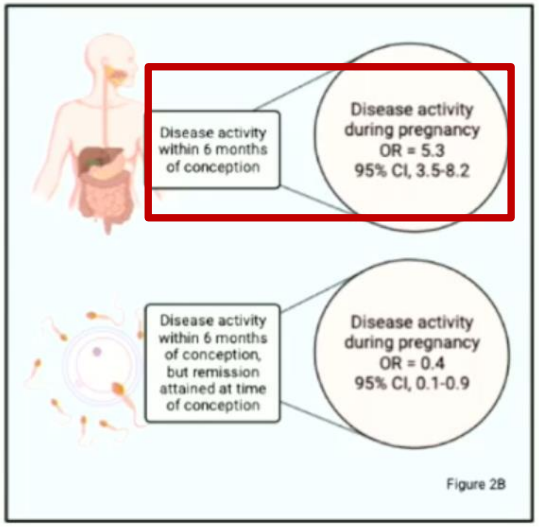
Bröms et. al. Inflamm Bowel Dis 2014; Torres et al. ECCO Pregnancy Guideline. JCC 2023

Predictors of disease activity during pregnancy

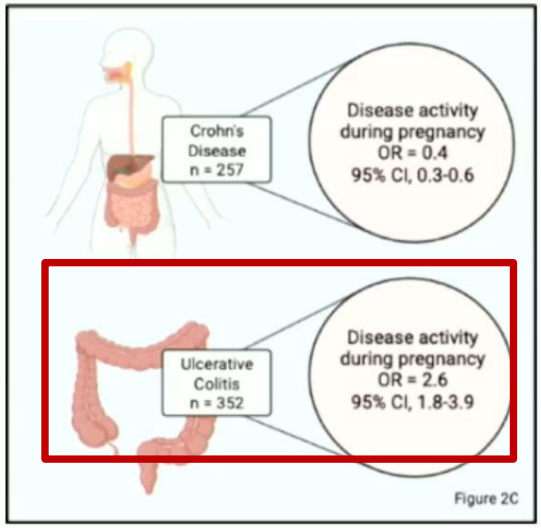
Previous pregnancy
OR 3.2 [95% CI, 1.5-6.6]



Activity prior to pregnancy
OR 5.3 [95% CI, 3.5-8.2]



IBD subtype
UC: OR 2.6 [95% CI, 1.8-3.9]



Vestergaard et. al. Aliment Pharmacol Ther 2023

Pregnancy: risk of disease activity

- Remission at conception → 19% risk of relapse in CD and 35% in UC
- In contrast to CD, increased risk of disease activity in UC during pregnancy
  - CAUSE:
    - Changes in immune tolerance during pregnancy?
    - Non-adherence rates to medical treatment is higher in UC than CD

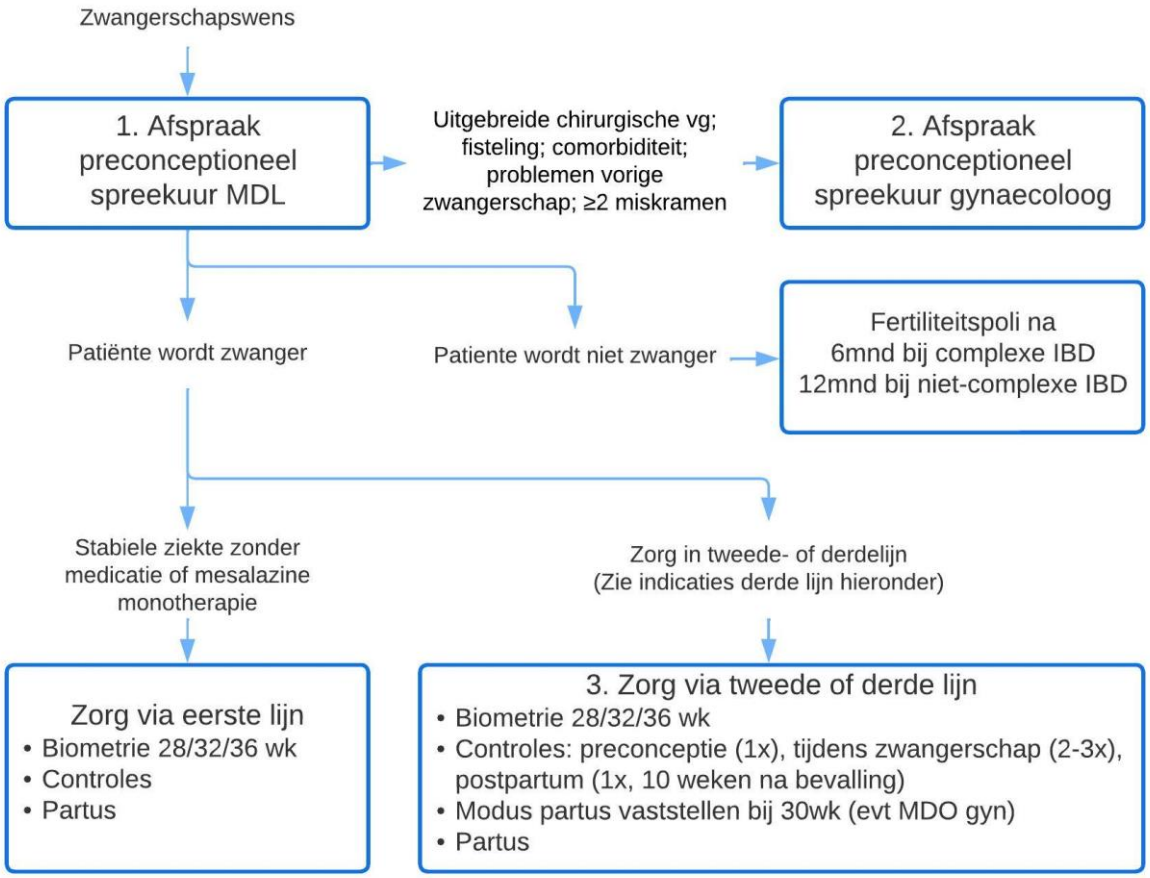
Pregnancy does NOT protect against risk of disease activity

Disease activity increase the likelihood of adverse pregnancy outcome

Strive for steroid-free remission 6 months prior to conception

Pedersen et. Al. Aliment Pharmacol Ther 2013, Julsgaard et al. Inflamm Bowel Dis 2011, Abhyankar et. Al. Aliment Pharmacol Ther 201

IBD*north* zwangerschapsprotocol

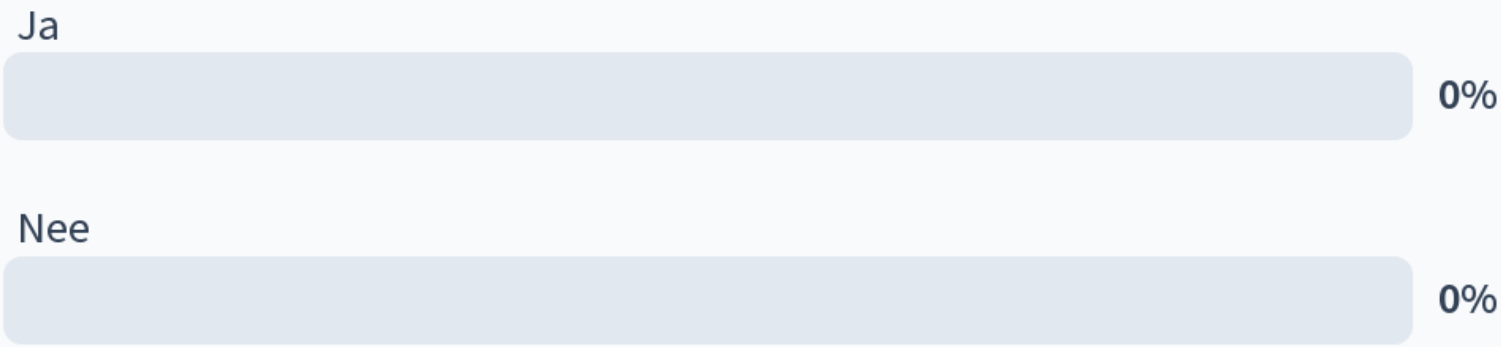


Overview of risks of drugs during the conception period

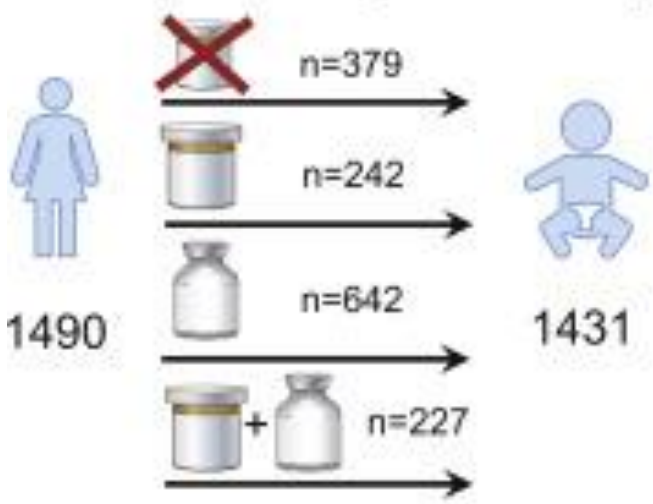
Drug[1,2]	Women	Men
Mesalazine*	Low risk	Low risk
*mesalazine compounds: phthalate-containing tablets are contraindicated due to ↑ risk of urogenital tract malformations and ↑ risk of impaired sperm quality		
Sulfasalazine	Low risk	Reversible oligospermia & ↓ sperm motility
Corticosteroids	Low risk	Low risk
Metronidazole	Low risk	Low risk
Ciprofloxacin	Low risk	Low risk
Thiopurines	Low risk	Low risk (does not impair sperm quality, but may impair sperm motility, no 6-TGN in sperm DNA)[3]
Thiopurines + allopurinol	Limited data	Limited data
Anti-TNF	Low risk	Low risk (does not impair sperm quality or sperm motility + negligible amounts in semen)[4]
Vedolizumab	Low risk	Low risk (does not impair sperm quality or sperm motility + negligible amounts in semen)[5]
Ustekinumab	Low risk	Low risk (does not impair sperm quality or sperm motility + negligible amounts in semen)[6]
Methotrexate	Contraindicated	Low risk (does not impair sperm quality or sperm motility + negligible amounts in semen)[7]
Tofacitinib	Contraindicated	No data. Animal studies: no impact on fertility, sperm motility or sperm concentration
Upadacitinib	Contraindicated	No data. Animal studies: no impact on fertility, sperm motility or sperm concentration[8]
Filgotinib	Contraindicated	Limited data. Animal studies: ↓ fertility, ↓ spermatogenesis & histopathological effect → Human studies (Manta & Manta-Ray): No impact on semen parameters or sex hormones[9,10]
Ozanimod	Contraindicated	No data. Animal studies: no impact on fertility, sperm motility or sperm concentration

1. Torres et al. ECCO Pregnancy Guideline. JCC 2023, , 2. Hammami MB and Mahadevan U. Am J Gastroenterol 2020 3. Grosen et. al. JCC 2018, 4. Grosen et. al. JCC 2019, 5. Grosen et al. Gastroenterology 2019, 6.Grosen et al Inflamm Bowel Dis 2022 7. Grosen et. al. Inflamm Bowel Dis 2021. 8. "use in pregnancy": AbbVie 9. Reinisch W et. al. Ann Rheum Dis 2023. 10. EMA 2023

To stop or not to stop? Moeten we biologicals in het 3e trimester stoppen?

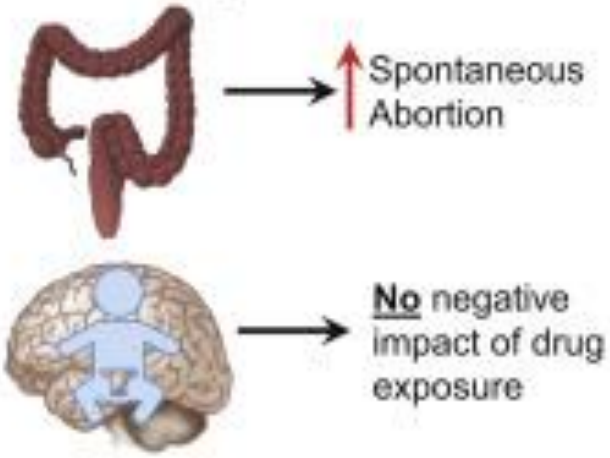


Pregnancy and Neonatal Outcomes after Fetal Exposure To Biologics and Thiopurines among Women with Inflammatory Bowel Disease



No increase in:

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



Gastroenterology

Infants of mothers receiving thiopurines or combination therapy had significantly increased birth weight.

There is no strong rationale to withhold biologic therapy in any pregnant IBD patient based on available evidence from PIANO and other international studies.

Medical treatment Flare

ECCO Statement 15

- Pregnant women experiencing a flare should be managed according to current guidelines for non-pregnant patients with 5-ASA, steroids, cyclosporine, 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].

Torres et al. ECCO Pregnancy Guideline. JCC 2023

Is it truly that simple?

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

CS Corticosteroids; OR Odds Ratio; T1 First Trimester

Odufalu FD, Long M, Lin K, Mahadevan U. *Gut* 2021. doi: 10.1136/gutjnl-2021-325317

Gut

Antenatal corticosteroids and serious infection in children born at full term

45.232 exposed vs. 1.915.313 non-exposed infants

- aHR 1.23 (95% CI, 1.15-1.32, p<0.001)

Yao T-C et. al. BMJ 2023

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Steroids can be used during pregnancy
- *in a wisely manner & <u>never</u> as maintenance treatment*

	Pregnancy	Offspring	Dosage
Budesonid/ budesonid MMX & Rectal prednisolon	Low risk	Low risk	Standard dosage
Prednisolon (**oral and IV**)	Moderate risk: gestational diabetes, PPROM	Preterm, SGA ↑ risk for infections at 9 and 12 months	Standard dosage – <u>shortest duration</u> Monitor mother & fetus

Disease activity is the strongest predictor for adverse pregnancy outcomes

Need to treat disease activity aggressively

- <u>Including induction therapy with biologics</u>

Healthy mother → healthy baby

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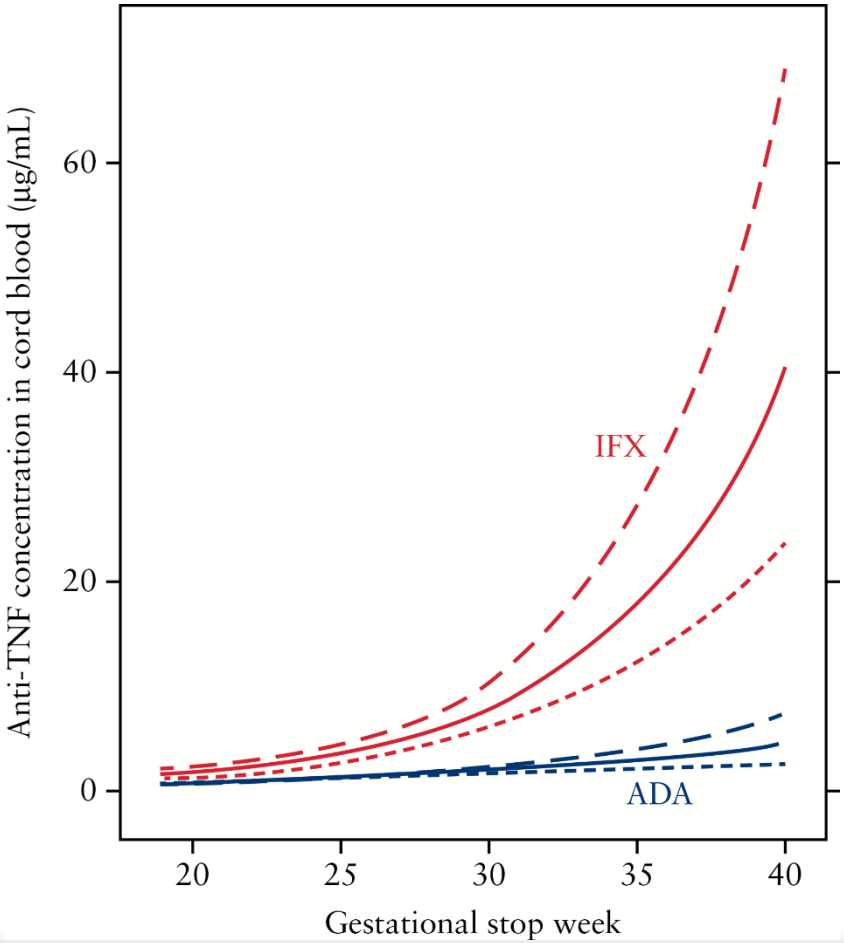
Spiegels anti-TNF te meten in navelstreng bloed



Anti-TNF Levels in Cord Blood at Birth are Associated with Anti-TNF Type
Kanis et al.
J Crohns Colitis. 2018;12(8):939-947. doi:10.1093/ecco-jcc/jjy058

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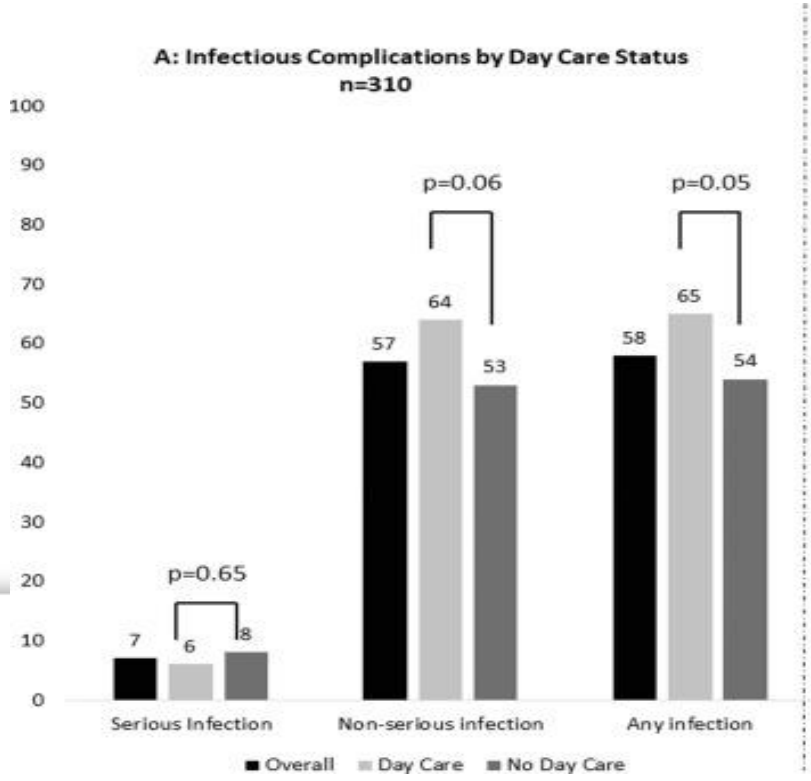
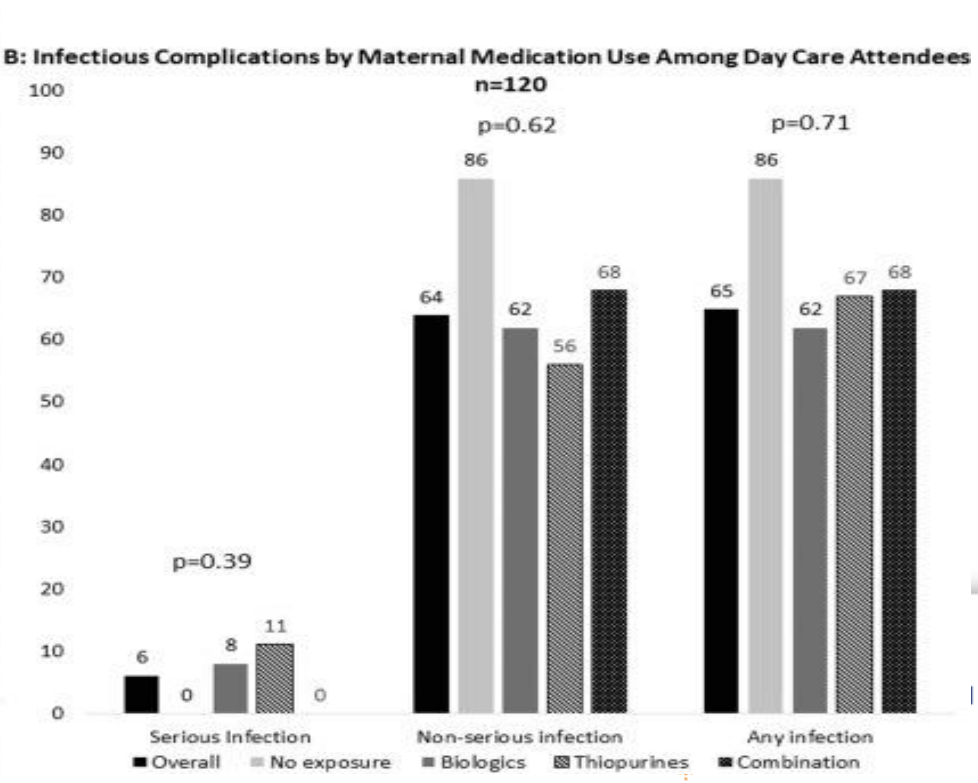
Post-partum

- UC; beducht voor postpartum exacerbaties (40% vs 19%)
- CD; geen verhoogd risico op exacerbaties, zelfs daling exacerbaties risico 5 jaar postpartum.





Breastfeeding

Drug	During lactation
Mesalazine	Low risk
Sulfasalazine	Low risk
Corticosteroids	Low risk
Metronidazole	Avoid
Ciprofloxacin	Low risk
Thiopurines	Low risk
Thiopurines + allopurinol	Limited data
Ciclosporin / Tacrolimus	Limited data
Anti-TNF	Low risk
Vedolizumab	Low risk, limited data
Ustekinumab	Low risk, limited data
Methotrexate	Contraindicated
Thalidomide	Contraindicated
Tofacitinib[2]	*Avoid*
Filgotinib	No data; avoid
Ozanimod	No data; avoid
Upadacitinib	No data; avoid

Statement 35 [1]

Drugs that are considered low-risk during pregnancy are also considered low-risk during breastfeeding and thus can be continued [EL3]

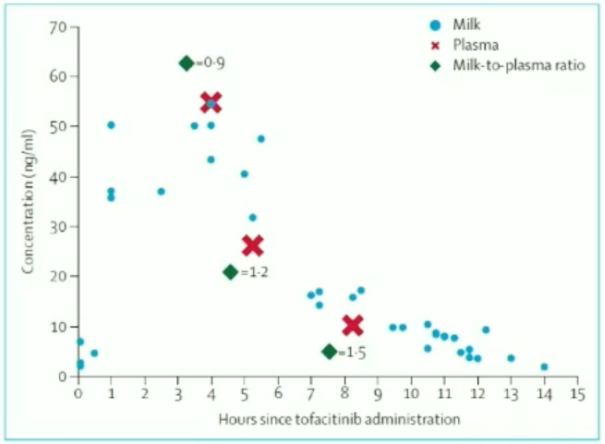


Figure: Tofacitinib concentrations in maternal milk and plasma
37 milk samples collected on 25 individual days during a 63-day period. [2]

Tofacitinib:

- After 4 hours: Milk concentration > plasma concentration[2,3]
- High infant exposure trough breastmilk[2,3]
- Normal immunological assessment in a 3 month old fully breastfed infant exposed to tofacitinib during pregnancy and via breastmilk[4]
- Avoid Tofacitinib during breastfeeding
  → pros and cons should be discussed with the patient

1. Adapted from Torres J et al. ECCO Pregnancy Guideline. JCC 2023, 2. Julsgaard M et. al. Lancet Gas Hep 2023, 3. Mitrova K et. al. Clin Gas Hep 2024, 4. Ernest-Suarez K et. al. Crohns & Colitits 360 2024.

Wat zijn potentiële complicaties van zwanger/bevallen met een stoma?

Nobody has responded yet.

Hang tight! Responses are coming in.

Pregnancy for IBD-patients with an ostomy is feasible, but is associated with complications

D.G. Bouwknegt, A.H.C. van der Weide, G. Dijkstra, W. van Dop, M.M.C. Hirdes, R.L. Goetgebuer, L. Oldenburg, J.R. Prins, F.J. Hoogenboom, C.J. van der Woude, M.C. Visschedijk

on behalf of the Dutch Initiative on Crohn and Colitis

Dept. of Gastroenterology and Hepatology, UMCG Groningen and ErasmusMC Rotterdam
Dept. of Colorectal Surgery, UMCG, Groningen, The Netherlands
Dept. of Obstetrics and Gynaecology, UMCG, Groningen, The Netherlands

INITIATIVE ON CROHN AND COLITIS

UMCG

Erasmus MC

ECCO

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66.1% ostomy-related complications

- 56 live births in 46 patients (49.2% UC; 50.8% CD)
- End ileostomy was the most prevalent stoma-type (77.0%)

Complications during pregnancy and postpartum* (n=56)	Pregnancies, n [% of cases]
Obstruction	16 [28.6]
Parastomal herniation	12 [21.4]
Prolapse	9 [16.1]
Minor complications	19 [38.0]
Total, n [% of cases]	**37 [66.1]**

*<1 year postpartum

Surgery during pregnancy	Pregnancies, n [% of cases]
Indication obstruction	2 [3.6]
Indication prolapse	2 [3.6]
Total	**4 [7.1]**

Postpartum surgery*	Pregnancies, n [% of cases]
Indication parastomal herniation	4 [7.1]
Indication prolapse	1 [1.8]
Total	**5 [8.9]**

Pregnancy outcomes

Caesarean section rate in IBD patients

	32.5% [5.7% – 80%]
	25.0%
Cohort	46.4%

Neonatal outcome (n=56)	Pregnancies, n [% of cases]
Premature (<37 weeks)	9 [16.1]
Low birthweight (<2500gr)	9 [16.1]
Small for gestational age (<10th percentile)	6 [10.7]

DDD
20 maart 2024
9.30 uur Brabant-zaal

D.G. Bouwknegt
rijksuniversiteit groningen
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Take home message

- Healthy mother = healthy baby
- Treat active disease, if necessary with biologicals
- Use steroids in wisely manner
- Multidisciplinary approach

Hebben jullie nog vragen? (mag digitaal of via de microfoon)

Nobody has responded yet.

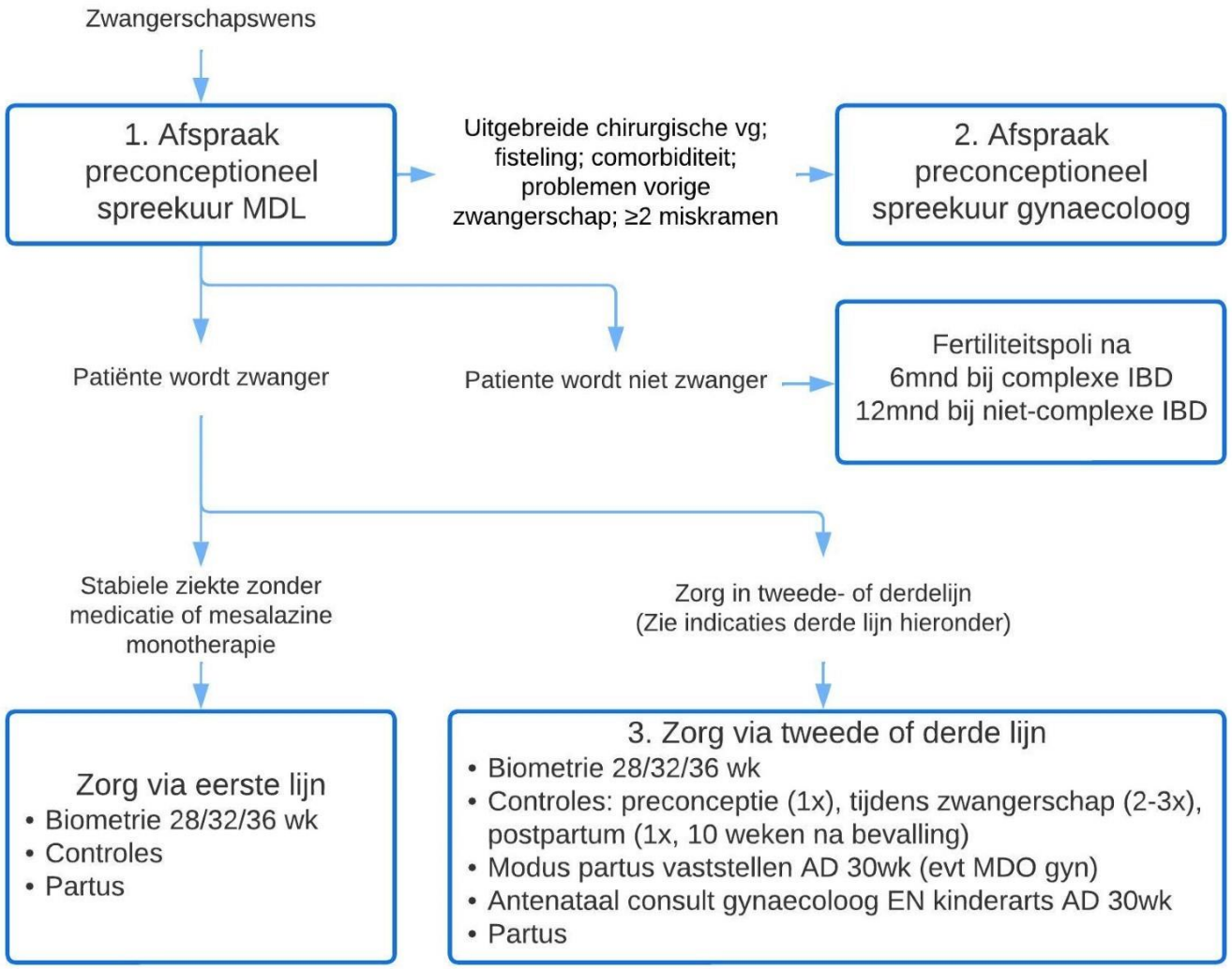
Hang tight! Responses are coming in.

Planning → Planner

De man

- Sulfasazine reduceert sperma motiliteit (reversibel)
- MTX reversibele oligospermie.
- Actieve ziekte of recent gesteld diagnose kan zorgen wel voor delay ~seksuele activiteit, sperma kwaliteit of beide.

- Mannen met IBD gebruiken meer medicatie tegen erectiele dysfunctie, dit is significant door operatiehistorie. (Friedman Am J Gastorenterol 2018)


Zwangerschapswens
1. Afspraak preconceptioneel spreekuur MDL
Uitgebreide chirurgische vg; fisteling; comorbiditeit; problemen vorige zwangerschap; ≥2 miskramen
2. Afspraak preconceptioneel spreekuur gynaecoloog
Patiënte wordt zwanger
Patiente wordt niet zwanger
Fertiliteitspoli na
6mnd bij complexe IBD
12mnd bij niet-complexe IBD
Stabiele ziekte zonder medicatie of mesalazine monotherapie
Zorg in tweede- of derdelijn
(Zie indicaties derde lijn hieronder)
Zorg via eerste lijn
• Biometrie 28/32/36 wk
• Controles
• Partus
3. Zorg via tweede of derde lijn
• Biometrie 28/32/36 wk
• Controles: preconceptie (1x), tijdens zwangerschap (2-3x), postpartum (1x, 10 weken na bevalling)
• Modus partus vaststellen AD 30wk (evt MDO gyn)
• Antenataal consult gynaecoloog EN kinderarts AD 30wk
• Partus

Preconceptie poli

Preconceptie adviezen:

- Vruchtbaarheid
- Ziekteactiviteit (minimaal 6 maanden rustig, dan groenlicht)
- Medicatie tijdens zwangerschap
- Borstvoeding
- Modus Partus
- Erfelijkheid

Maar ook: foliumzuur gebruik en roken

Preconceptie poli

- N=155 vs N=162 (controle)
- Minder exacerbaties (onafhankelijk van eerdere ziekteactiviteit), (aOR, 0.51)
- Medicatietrouwer (aOR, 5.69)
- Rookten minder (aOR, 4.63)
- Minder baby's met te laag geboortegewicht (aOR, 0.08)

Fecundity/Fertility considerations in patients with IBD

Voluntary childlessness[1]

- 18% IBD vs. 6% background population
- Incorrect beliefs and insufficient knowledge

Surgery

Women:

- **CD:** unclear impact[4], prolonged (>12mo) time to conceive[5]
- **UC:** IPAA - x3 risk of infertility (adhesions)[6]
- Minimal invasive surgery - lower infertility rates[7]

Men:

- IPAA surgery: 3% risk of retrograde or no ejaculation[8]
- Retrograde ejaculation → Assisted Reproductive Technology (ART) is an option

Remission + no surgery

UC or CD

Fertility rate equals general population[2]

CD women: Age >30, reduced ovarian reserve (↓ AMH)[3]

Severe activity in IBD

Women:

- Active Crohn's disease - infertility ↑[9]

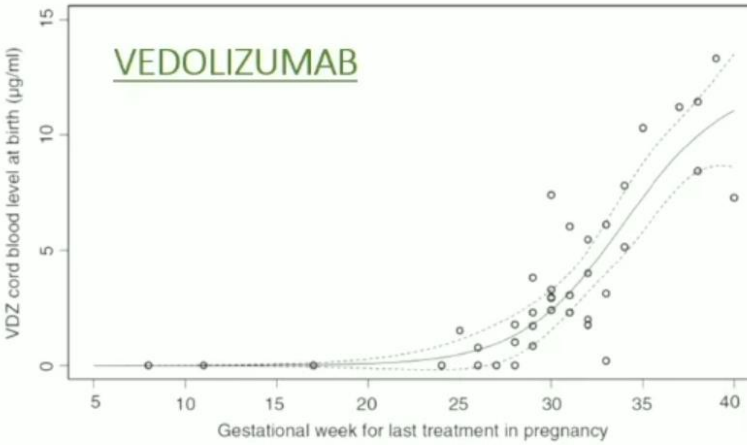
Men:[10]

- Slight ↓ progressive sperm motility
- ↓ testosterone levels
- Sperm DNA integrity is unaffected

Early referral for infertility evaluation should be considered depending on age, type of disease, and prior surgery

1.Marri et al, Inflamm Bowel Dis; 2007. 2. Tavernier et al , Aliment Pharmacol Ther 2013. 3 Freour T et al, Inflamm Bowel Dis 2012 4. Lee et al ; Cochrane Database of Systematic Reviews 2019. 5. Friedman et al ; Clin Gastro Hepatol; 2020 6. Waljee et al ; Gut 2006. 7. Bartels et al ; Ann Surg. 2012 8. Farouk R et. al. Ann Surg 2000. 9. Druvefors et al ,JCC 2020 10. Grosen A et. al. JCC 2019

Biologics and Pregnancy



- Normal pregnancy outcome & infant development
- Maternal IFX clearance ↓ in the 2nd & 3rd trimester; ADA ↔
- Inverse relationship: infant drug level & timing of last dose
- Infant & maternal levels at delivery:
  - Increased infant levels: IFX (↑ ↑ ↑), ADA (↑ ↑) & UST (↑ ↑)
  - VDZ infant level 50%↓ compared with maternal level

- No correlation between birth level of biologic and risk of infant infection

- Maintain pre-pregnancy dosing & continue throughout pregnancy
- Plan final dose according to half-life to minimise biologic transfer to the infant
- Overall benefits of maintaining remission outweigh any potential ↑ risk of treatment

Maternal clearance: Grisic et. al. UEG Journal 2020, Flanagan et. al. AP&T 2020, Seow et. al. AP&T 2017.
Anti-TNF: Kanis et. al. JCC 2018, Julsgaard et. al. Gastroenterology 2016, Mahadevan et. al. Gastroenterology 2020.
UST & VDZ: Julsgaard et. al. AP&T 2021, Julsgaard et. al. Clin Gas hep 2023. Chugh et. al. Am J G

Monitoring disease activity during pregnancy

Prompt identification and treatment of an IBD flare during pregnancy is important
General approach to IBD flare - comparable to the non- pregnant patient

Biomarkers

Normal physiological changes during pregnancy

Parameter	Change
Leukocyte count	↑
Hemoglobin	↓
ESR	↑
CRP	↑
Albumin	↓

Fecal calprotectin

Not affected by pregnancy[2]

Effectively asses disease activity throughout pregnancy (FC>250 - PGA) [2,3]

Imaging & Endoscopy

✓ Intestinal ultrasound[4,5]
(Especially during the 1st & 2nd trimester)
✓ MRI - without the use of gadolinium
(✓) CT - to assess suspected acute complication

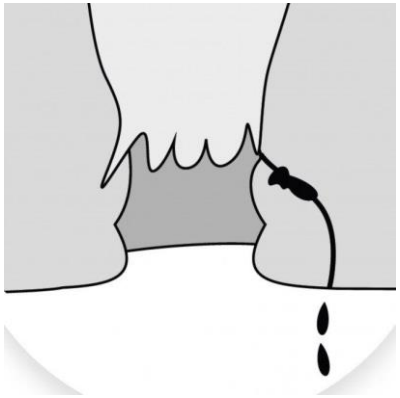
✓ Endoscopy [6,7]
When needed to guide clinical decision

✗ Capsule endoscopy[8]

1. Torres J et al; Journal of Crohn's and Colitis, 17 (1) 2023, 1–27 2. Julsgaard M et al; IBD J; 2017. 3. Kammerlander H et al; IBD J; 2018; 4. Flanagan E et al; JCC; 2020 .5. De Voogd F; IBDJ; 2022 6. Flanagan E et al; Best Pract Res Clin Gastro; 2020. 7 Van der Woude C.J et al; JCC;2015;107-124; 8. Rondonotti E et al, Endoscopy,2018

Background: ECCO guidelines

+

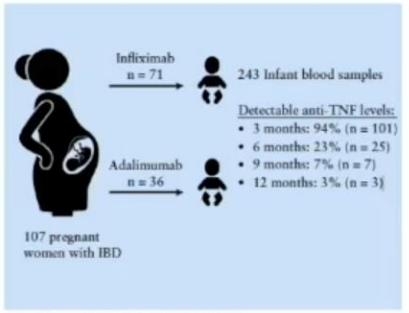


Crohn's disease + perianal fistulas

<u>Active</u>: indication caesarean section

<u>Inactive</u>: multidisciplinary, governed by obstetric indication

Vaccines in infants exposed to biologics *in utero*



Liu, Julsgaard, et al. *J Crohns Colitis*

Inactivated vaccines[1]:

Recommended according to national guidelines

- No adverse events, adequate serologic response[5,6]

Biologic In utero	Mean Time to drug clearance [2,3,4]
Infliximab	7.3 months (95% CI, 6.2-8.3)
Adalimumab	4.0 months (95% CI, 2.9-5.0)
Vedolizumab	3.8 months (95% CI, 3.1-4.4)
Ustekinumab	6.7 months (95% CI: 6.1-7.3)

Live attenuated vaccines:

Rota virus (2,4 months), BCG (4th day-6weeks), Oral polio (2,4,6months)

- BCG - 5 cases of death - disseminated BCG infection (Anti-TNF)
- Vedolizumab and ustekinumab - can be administered from 6 months of life
- Anti-TNF - avoid for 12 months of life or until a blood test confirms clearance
- Increasing data on the safety of rotavirus vaccine administraion to infants exposed to biologics in utero[7,8,9]

  Canadian Special Immunization Clinic - 191 infants exposed to biologic agents throughout pregnancy, no clinically significant immunological abnormalities (lymphocyte subsets, quantitative immunoglobulins, mitogen responses) and no significant adverse events after immunization[6]

1 Torres et al; JCC;2023. 2. Julsgaard et al Gastroenterology 2016 3. Julsgaard M et al Aliment Pharmacol Ther. 2021 4. Julsgaard M et al; Clin Gastro Hepatol 2024. 5. de Lima et.al. JCC 2018. 6. Beaulieu et.al. CGH 2018
7. Fitzpatrick et al; Lancet Child Adolesc Health 2023 8. Jisbert, Chaparro United Eur Gastroenterol J 2022. 9. Benchimol et al; Gastroenterology 2021

Key principles during pregnancy

- Healthy mother → healthy baby!
- Be clear on the impact of active disease during conception and pregnancy
- Treat active disease – if needed induction treatment with biologics
- Biologics as maintenance treatment in pregnancy
- Corticosteroid can be used to treat flare → shortest duration, maintenance strategy
- Multi-disciplinary approach
- Shared decision-making

Thank you for your attention