IBD | Pregnancy

Klaartje Bel Kok – Royal London Hospital

Aileen Fraser – Bristol Royal Infirmary

Ferring National IBD Doctors Annual Meeting

24th September 2021

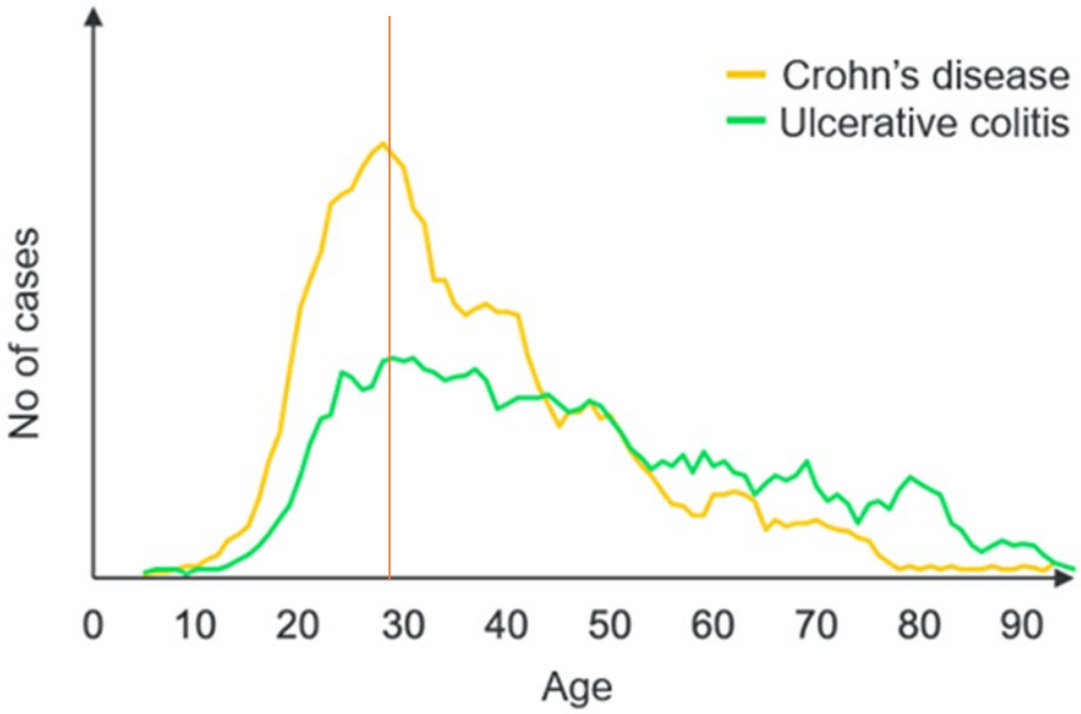
Date of preparation: Sept 2021 – UK-GAS-2100099

Disclosures

- Dr Kok
- Speaker fees – Takeda, Ferring
- Advisory board - Janssen, PredictImmune, Amgen, Galapagos
- Travel – Janssen, Takeda

- Ms. Fraser

Why is this important



Bortoli et al. Aliment Pharmacol Ther 2011

Question

How many of the audience have access to a Joint IBD antenatal clinic?

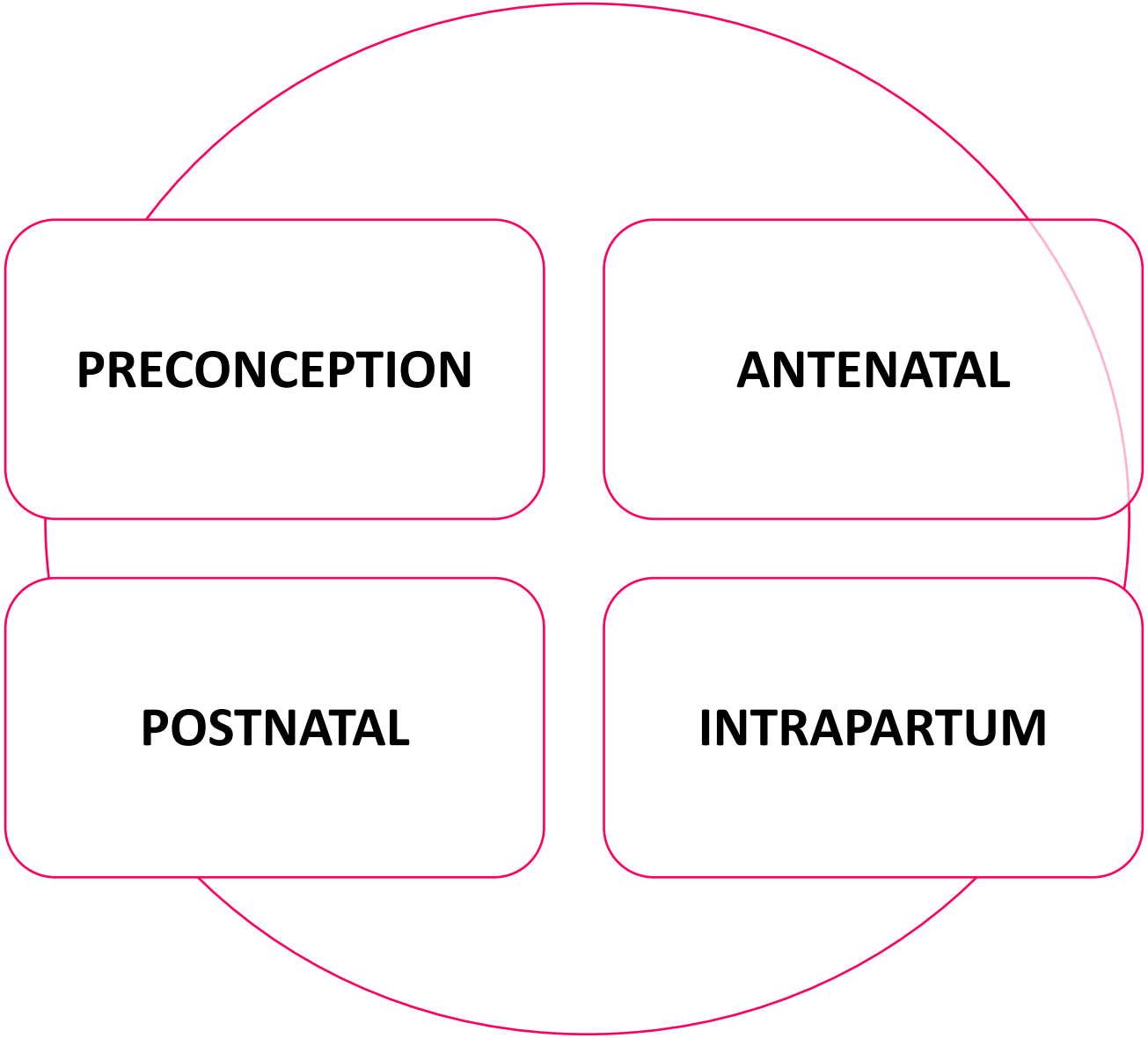
1 Yes

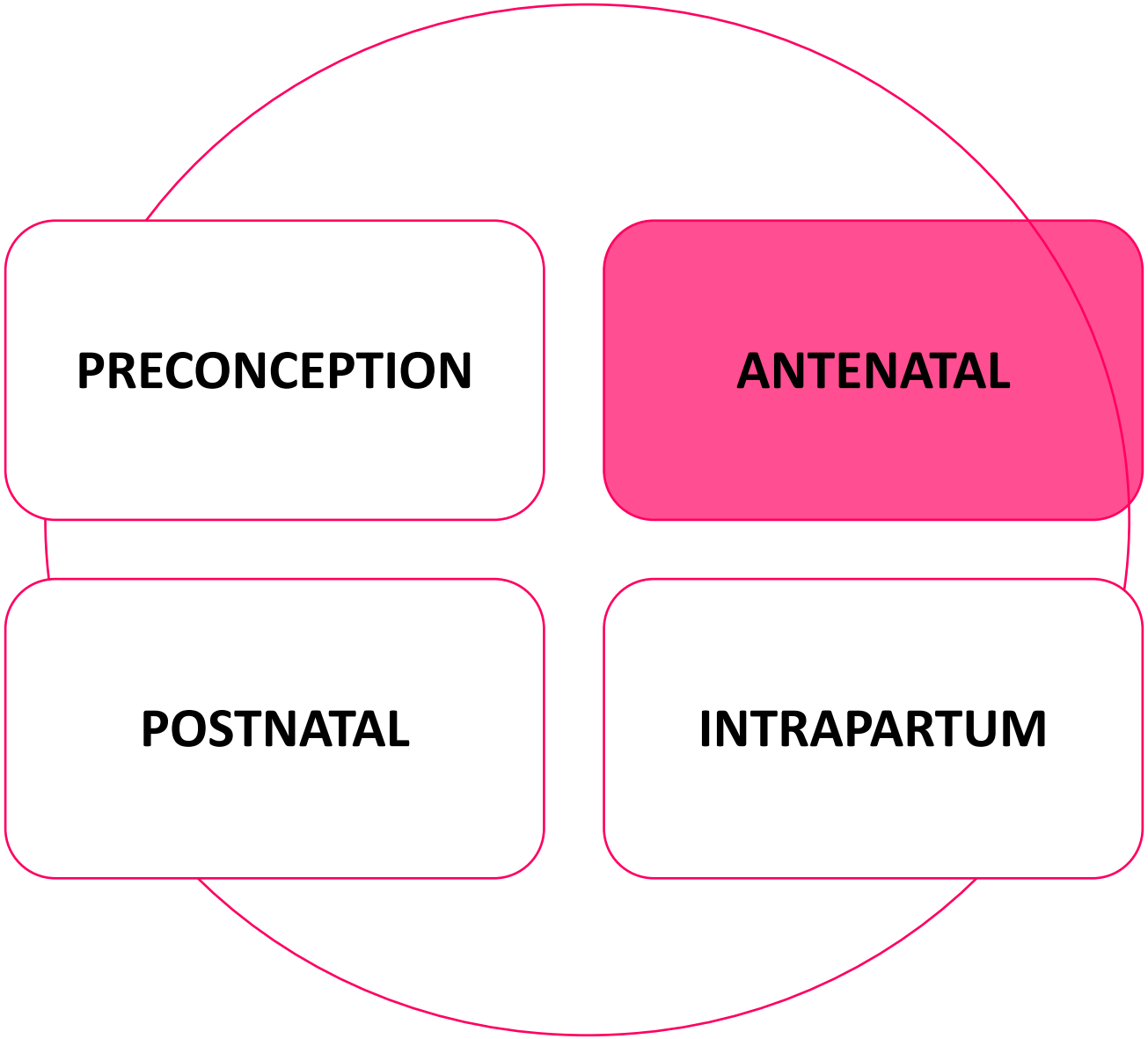
14%

2 No

86%

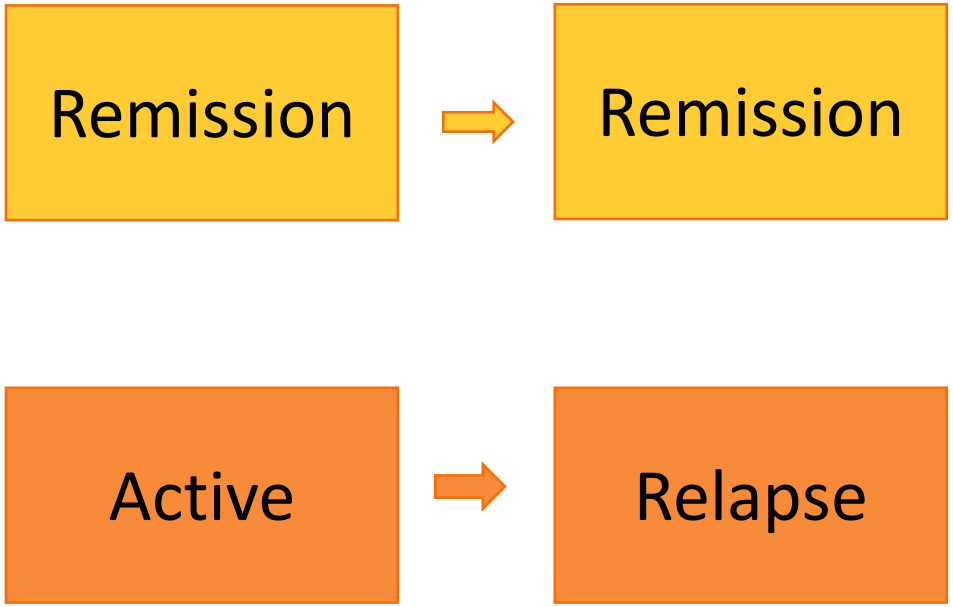
Vote Now


PRECONCEPTION
ANTENATAL
POSTNATAL
INTRAPARTUM



1/5 stop medications

Effect pregnancy on IBD



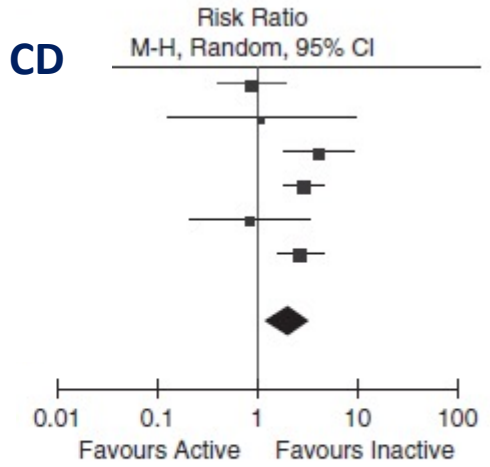
Abhyankar et al. Aliment Pharmacol Ther 2013

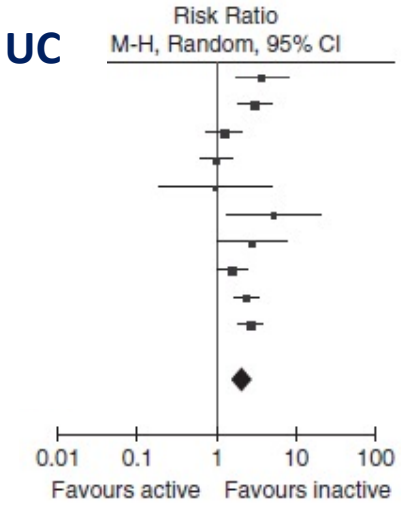
Effect IBD on pregnancy

Remission → No complications

Active →
- poor growth
- low birth weight
- preterm delivery
- miscarriage 1st trimester
- emergency caesarean

Cognitive function, behaviour





Meyer A, UEGW 2020 - OP015; Zelinkova et al, Scand J Gastroenterol 2010

Medication safety

• Sulfasalazine • Mesalazine	• Azathioprine • 6-Mercaptopurine • Methotrexate • Tofacitinib	• Infliximab • Adalimumab • Vedolizumab • Ustekinumab • Certolizumab	• Budesonide • Prednisolone • Hydrocortisone • Tacrolimus • Ciclosporin

5-aminosalicylates

Congenital abnormalities	OR 1.16 (95% CI: 0.76-1.77, P=0.57)
Stillbirth	OR 2.38 (95% CI: 0.65-8.72, P=0.32)
Preterm delivery	OR 1.35 (95% CI: 0.85-2.13, P=0.26)
Spontaneous abortion	OR 1.14 (95% CI: 0.65-2.01, P=0.74)
Low birth weight	OR 0.93 (95% CI: 0.46-1.85, P=0.96)

Sulfasalazine – Folic acid: 5 mg per day

Rahimi Reprod Toxicol 2008; Colombel Lancet 1994

Methotrexate

Methotrexate has been reported to cause fetal death and/or congenital anomalies.Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant women with psoriasis or rheumatoid arthritis should not receive methotrexate. (See **CONTRAINDICATIONS**).

Avoid in pregnancy

Stop **3** months before conception

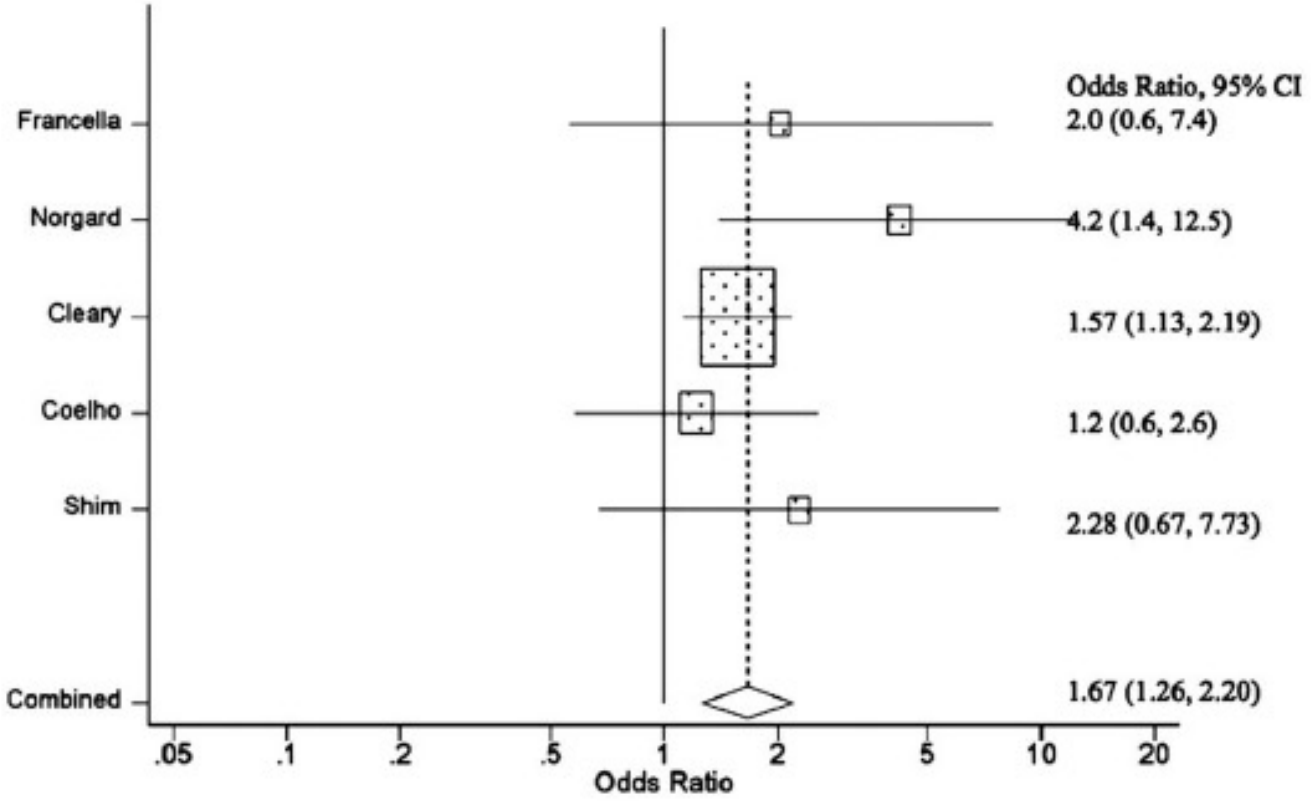
Do not breastfeed on methotrexate

Mahadevan U, Gastroenterology 2017;152:451–462

Thiopurines

Meta-analysis and systematic review

Maternal thiopurines use and preterm birth



- Congenital anomalies – OR 1.45 (95% CI 0.99, 2.13)
- Low birth weight – OR 1.01 (95% CI 0.96, 1.06)

Low risk

!Metabolites altered

Akbari et al., Inflamm Bowel Dis 2013

Question

Which monoclonal antibody will NOT cross the placenta?

1 Ustekinumab

2.4%

2 Vedolizumab

14.3%

3 Risankizumab

0.0%

4 Certolizumab

81.0%

5 Adalimumab

2.4%

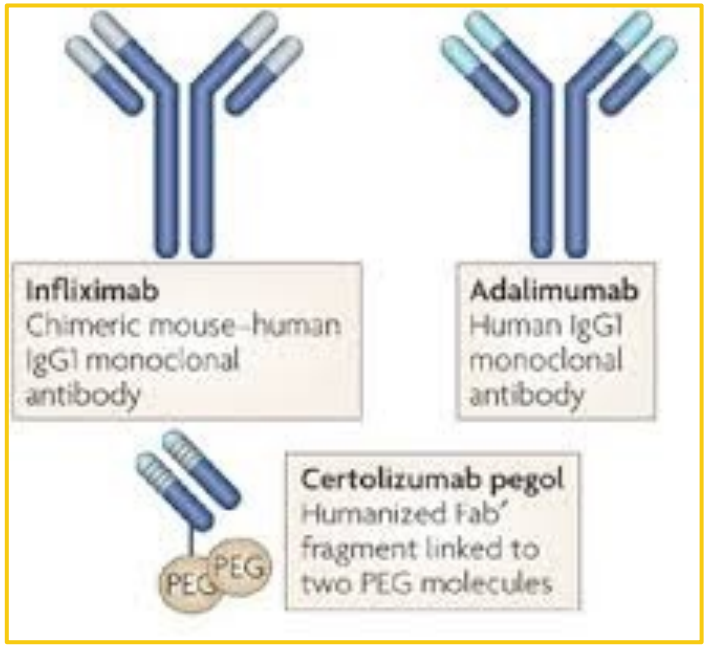
Vote Now

10

Anti-TNFs

- IgG1 – cross placenta
- Higher relapse rates when anti-TNF stopped
- Live vaccines not safe for 6 months (all biologics)

✓Safe – pregnancy and neonate



Mahadevan U, Gastroenterology 2019;156:1508–1524

Vedolizumab

- Increasing number of studies showing no adverse effects
  - Normal milestones
  - No increased infections
  - Risk of infection not correlated with cord levels

✓Live vaccines after 6 months

Juulsgaard, UEGW 2020 OP15

Ustekinumab

- Safe in high dose primate studies
- No increased risk from small series, isolated case reports and clinical trials programme
  - psoriasis or psoriatic arthritis = much lower dose

Mahadevan U, Gastroenterology 2019;156:1508–1524

JAK inhibitors - Tofacitinib

- Small molecule - likely can cross the placenta
- Teratogenicity in animal models
  - Limited number of maternal and paternal exposures from clinical trials programmes and post-approval safety studies - no increased risk identified
- Manufacturer recommendation to use contraception during treatment with tofacitinib and 4-6 weeks after the last dose

⇒ Avoid or use with caution

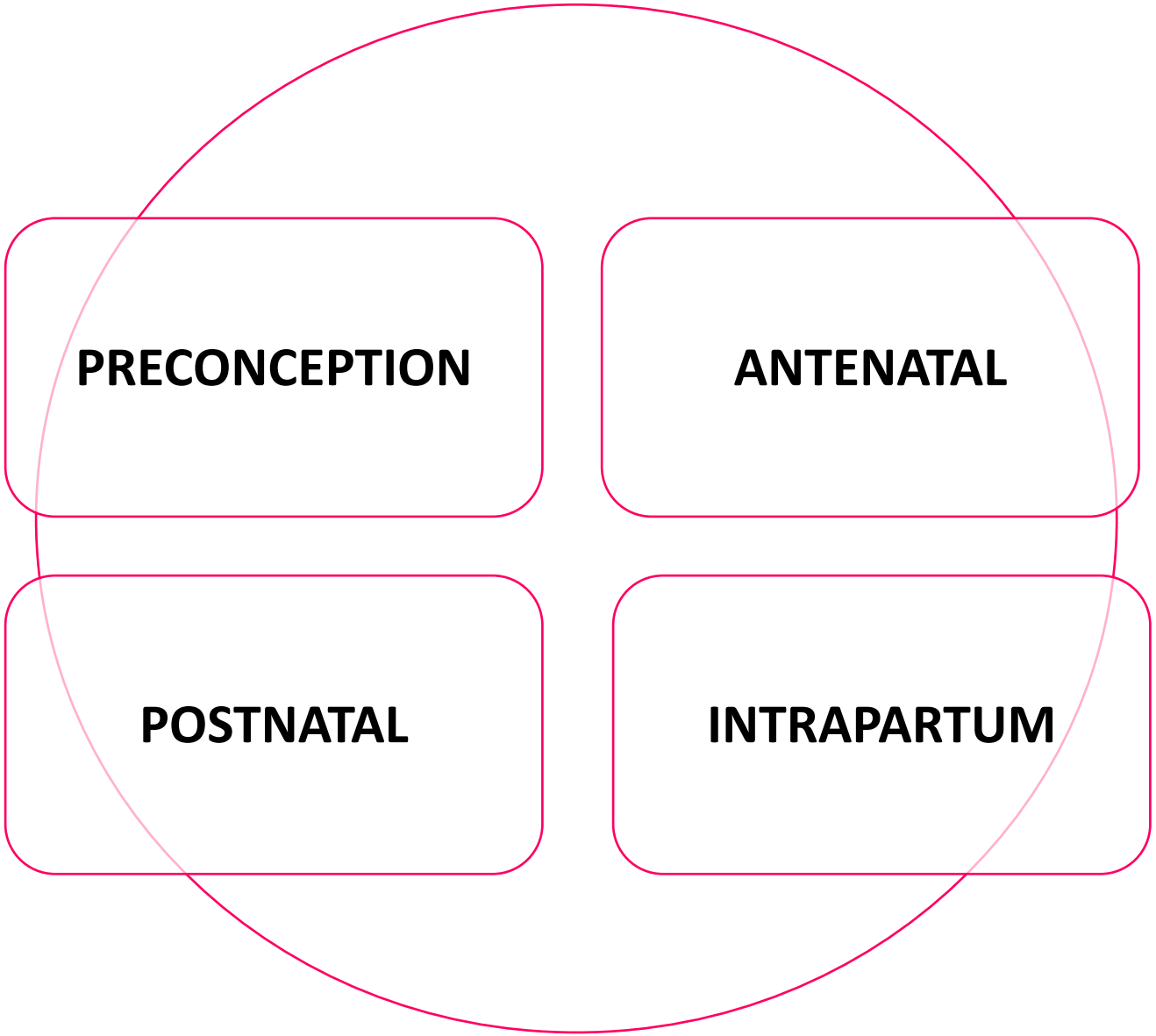
⇒ Do not breastfeed on tofacitinib

Drugs and Lactation Database (LactMed)

Medication safety

• Sulfasalazine • Mesalazine	• Azathioprine • 6-Mercaptopurine • Methotrexate • Tofacitinib	• Infliximab • Adalimumab • Vedolizumab • Ustekinumab • Certolizumab	• Budesonide • Prednisolone • Hydrocortisone • Tacrolimus • Ciclosporin

Lan Le Hoang, Ther Drug Monit 2020; Paziana, Drug Saf. 2013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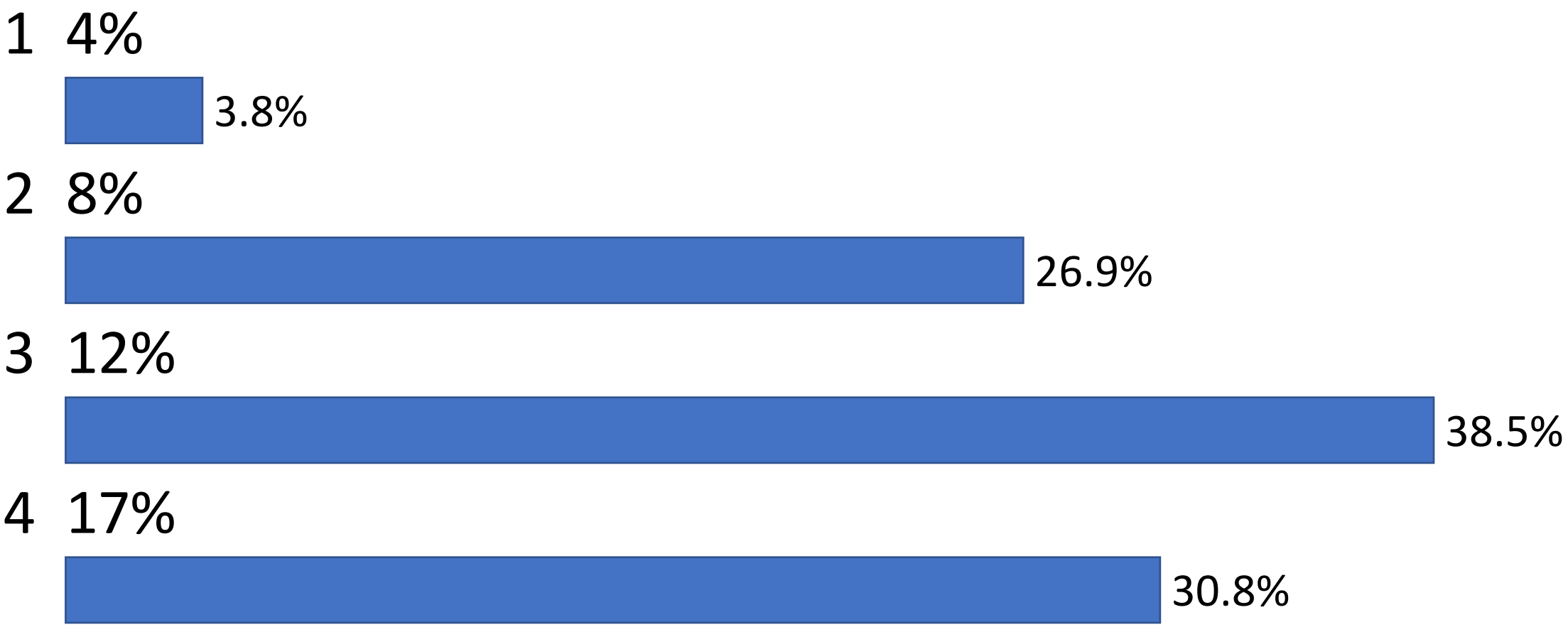
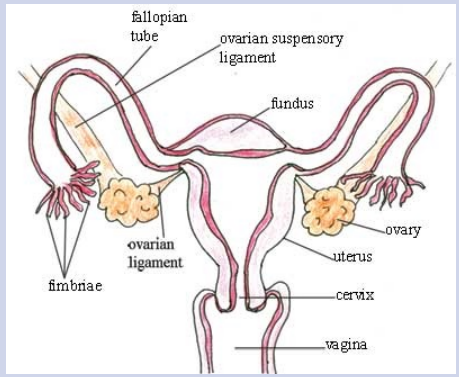
Question

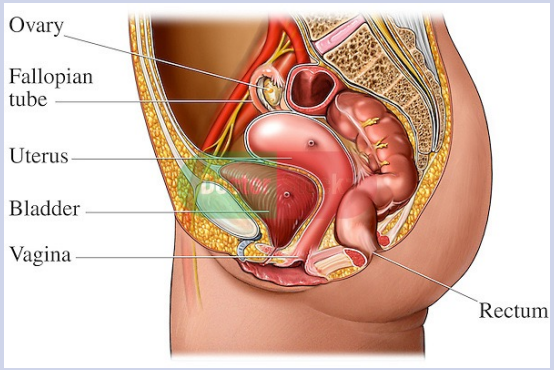
What are the rates of voluntary childlessness in women with IBD

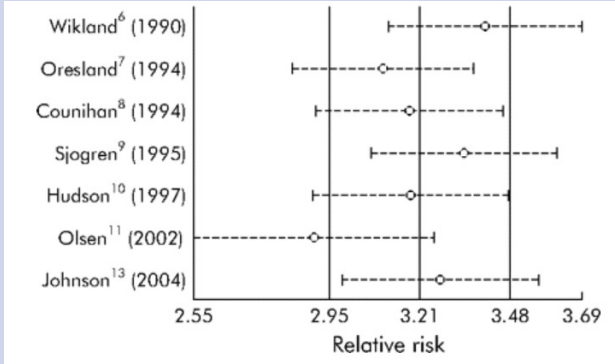


Female fertility

Normal fertility	Subfertility	Reduced fertility
Ulcerative colitis Crohn's disease Remission, without prior surgery All medical therapy for IBD voluntary childlessness **17% vs 6%**	Active disease Inflammation fallopian tubes Poor nutrition Depression Decreased libido, body image Dyspareunia	Ileal pouch anal anastomosis Pelvic surgery Scarring fallopian tubes Laparoscopic IPAA surgery better compared with open IPAA surgery







Selinger CP et al. Frontline Gastroenterol. 2020 May 19;12(3):214-224

Question

Men with IBD are likely to have?

1 Usually do not have problems with infertility

96%

2 Should avoid all medication when trying for a baby

2%

3 Should not have children with women suffering from IBD

2%

4 Should not father children after the age of 40

0%

Vote Now

Male fertility

Normal fertility	Subfertility	Not known	Sexual function
Ulcerative colitis Crohn's disease Remission	Active disease Poor nutrition Depression Decreased libido	IPAA Pelvic surgery	After IPAA may experience erectile dysfunction and retrograde ejaculation Overall same or improved sexual function after surgery

Male patients with IBD also have fewer children compared with the general population

Refer IBD patients for fertility evaluation if they have unsuccessfully tried to conceive for 6-12 months

Selinger CP et al. Frontline Gastroenterol. 2020 May 19;12(3):214-224

Medications and male fertility

SULFASALAZINE

- Reversible, dose-related decrease in both sperm count and motility

⇒ switch to a different 5-ASA

CORTICOSTEROIDS

- Reversible decrease in sperm motility and concentration
- No link between steroid use and infertility

METHOTREXATE

- Causes reversible oligospermia
- Paternal exposure **not** teratogenic

AZATHIOPRINE

- Does not reduce semen quality
- No increased congenital abnormalities

ANTI-TNFs

- Not extensively studied
- Cessation before conception not recommended

NEW AGENTS

- Tofacitinib and ustekinumab - no data – healthy babies from exposed fathers
- No adverse effects in animal studies

Mouyis M, Semin Arthritis Rheum. 2019

Question

Women with inflammatory bowel disease

1 Should never have a caesarean section?

2%

2 Can have a vaginal delivery in most cases?

91%

3 Must have a caesarean section?

0%

4 And peri-anal disease are advised against having a C- section?

7%

Vote Now

Partum – individual approach by MDT

- Mother's choice
- Caesarian in - **active** perianal Crohn's disease
  - IPAA relative indication
- Post-partum VTE if active disease

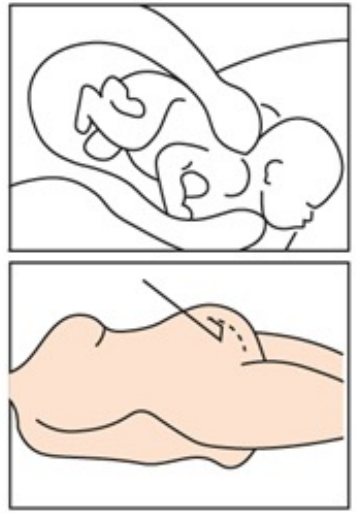


TABLE 3. Multivariate analysis for associations with 4th degree perineal laceration

	OR	*95% CI*	*p*
Age	0.99	0.98–0.99	<0.001
Smoker	1.58	1.5–1.7	<0.001
Crohn's disease	1.18	0.8–1.8	0.4
Perianal disease	10.86	8.3–14.1	<0.001
Episiotomy	0.61	0.6–0.6	<0.001

Hatch et al., Dis Colon Rectum 2014

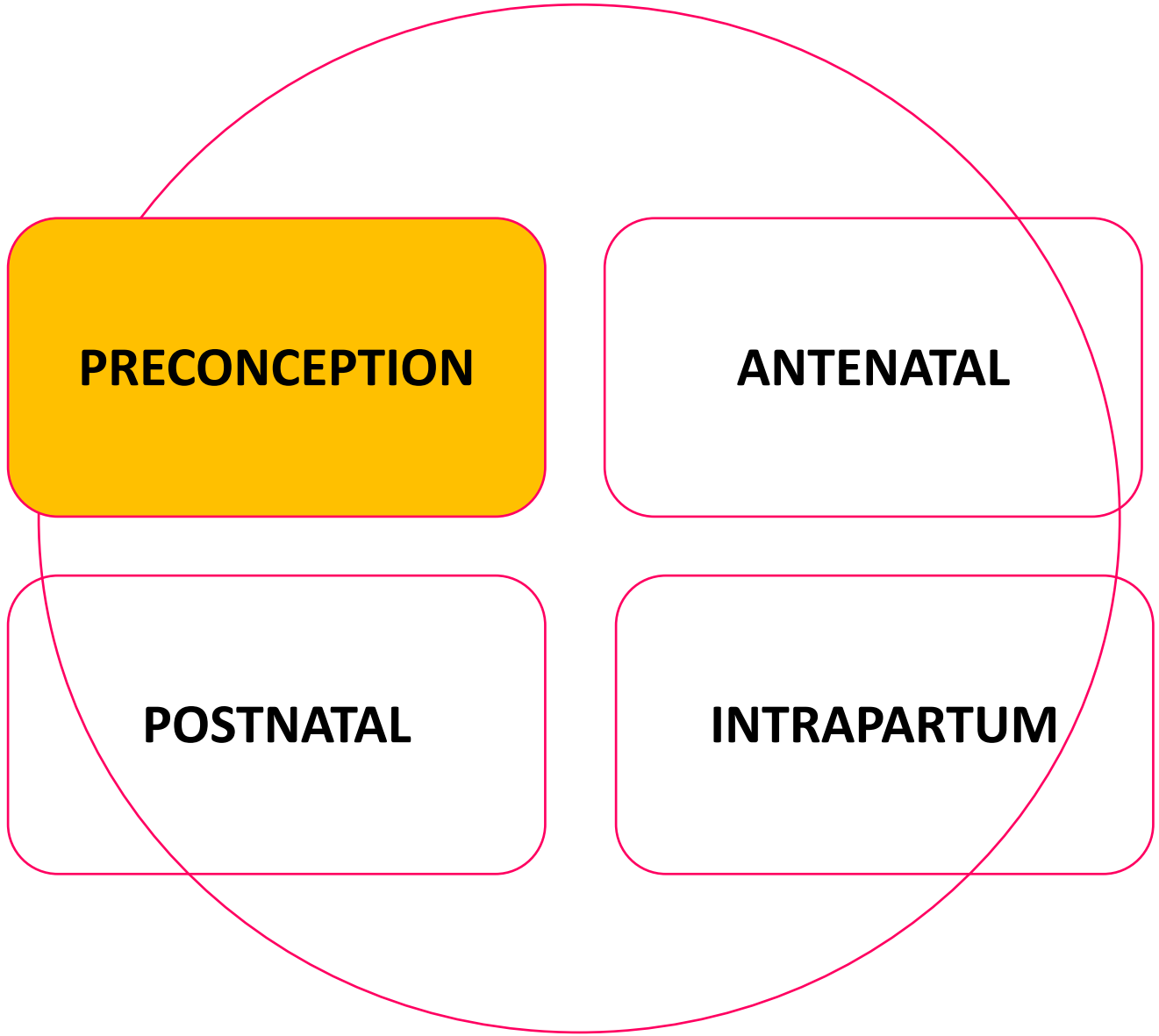
Postnatal - No increased risk of flare

- One third of IBD patients experience a flare after delivery
  - No higher than the overall risk of a disease flare while not pregnant

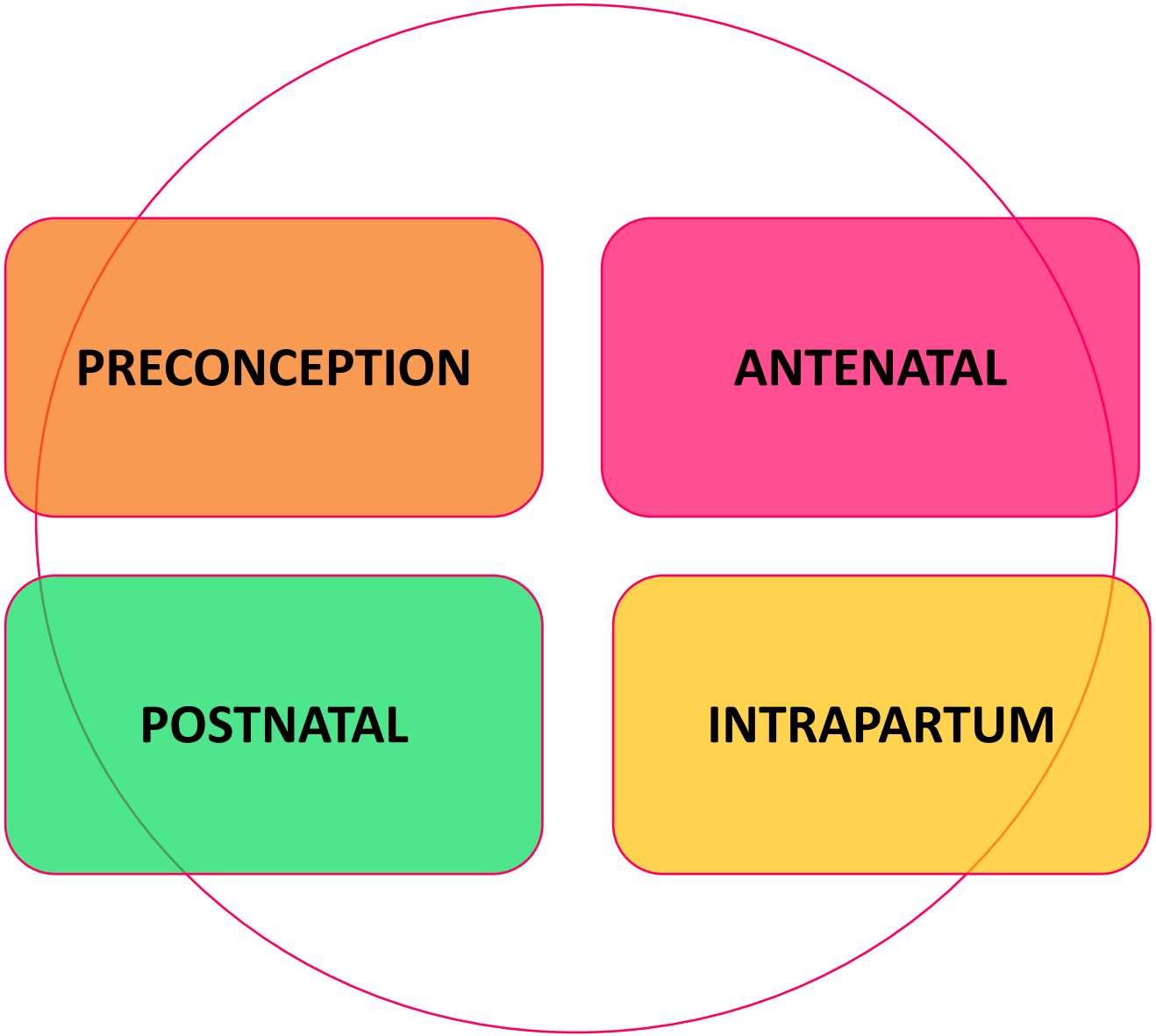
- Risk of a disease flare is not increased by breastfeeding

- Breastfeeding confers a duration-dependent protection against the development of IBD

Crohn's disease	Ulcerative colitis
OR 0.45 (95% CI 0.26–0.79)	OR 0.56 (95% CI 0.38–0.81)



- Contraception, preconception advice – an afterthought..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1. Preconception

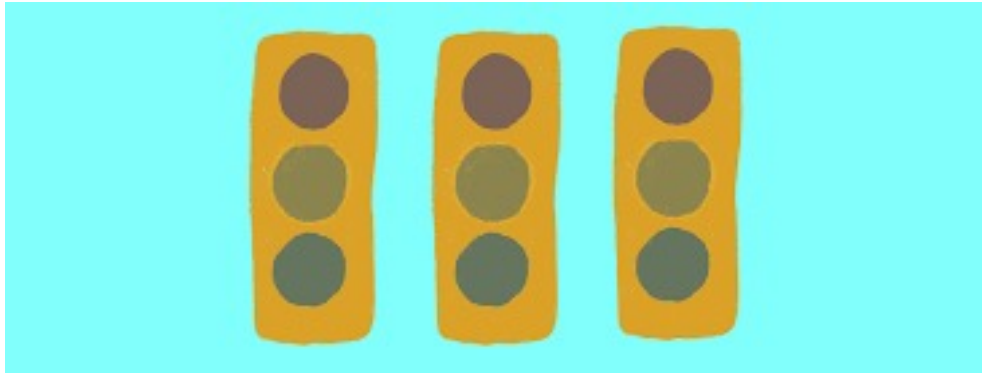
- Education throughout
- Dedicated preconception counselling for some

Remission

Remission

Remission

- Ask about contraception!



2. Antenatal

- Dedicated clinic

- Medications; 3 trimester biologic use. Stop date
- Extra growth scans
- VTE risk
- Birth plan
- Vaccination – neonate and mother
- Breastfeeding
- Contraception plan

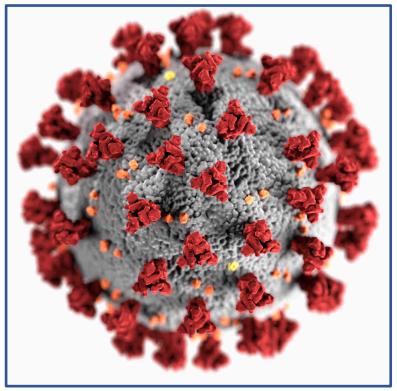
4. Postnatal

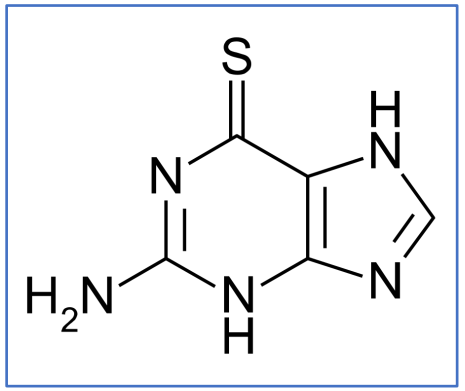
- Breastfeeding confers a duration-dependent protection against the development of IBD

Crohn's disease	Ulcerative colitis
OR 0.45 (95% CI 0.26–0.79)	OR 0.56 (95% CI 0.38–0.81)

- Restart medications immediately

- Biggest risk is active disease
- What is good for mother, is good for the baby
- Educate, ask about contraception
- Monoclonal antibodies safe

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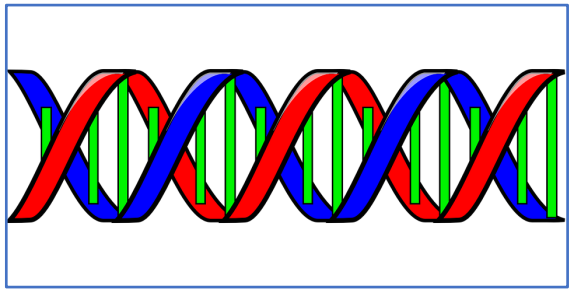
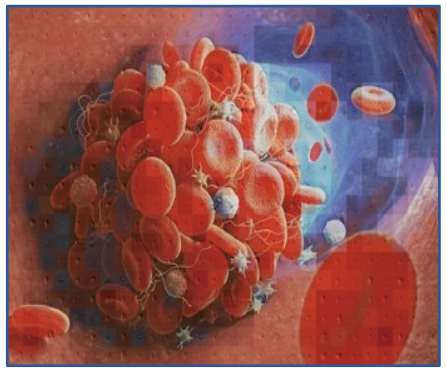
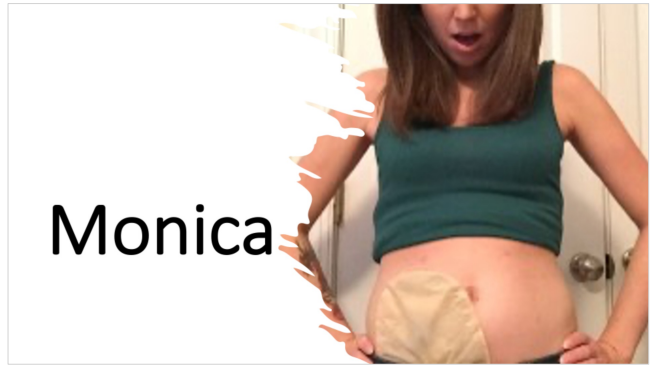
Katie

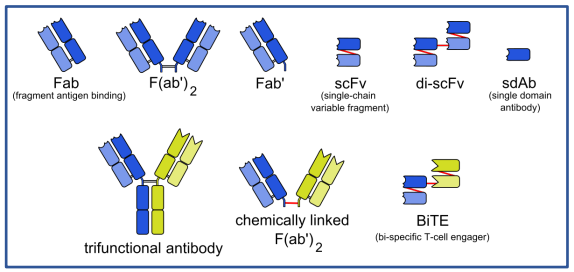

TAKEAWAY


Syeda






Monica


Fab
(fragment antigen binding)
F(ab')2
Fab'
scFv
(single-chain variable fragment)
di-scFv
sdAb
(single domain antibody)
trifunctional antibody
chemically linked F(ab')2
BiTE
(bi-specific T-cell engager)

Katie

Katie 33 years old

February

Diagnosis:

1. Crohn's disease diagnosed January 2006
2. Colonic disease with perianal involvement
3. Formation of ileostomy 2012
4. Current labial and groin fistulas also

Treatment

Azathioprine 150mg

Adalimumab 40mg EOW (Previously lost response to Infliximab)

IBD CNS

- Discussion with CNS following consultant consultation
- Relationship problems due to perianal disease
- Doesn’t feel feminine
- Referral to liaison psychiatry due to low mood.

June

10/40 - Congratulations!

Plan

Stay on the medication

Plan to stop adalimumab in 3rd trimester

Referred to obstetrics

July/Aug 2014

Contact from KN – fistulas more active – commenced erythromycin (penicillin allergy)

ED visit and I&D of abscess

Reviewed in IBD surgical clinic – MRI and swab

MRI Conclusion: Complex multiple fistulae the appearances have worsened compared to the previous study as described

August / September

Plan

Antibiotics – options

- Co-trimoxazole - but only in 2nd trimester 14-28
- Metronidazole
- Clindamycin
- Ciprofloxacin

Commence LMWH

Anti-TNF?

- Continue adalimumab throughout pregnancy

Sept – Nov 2014

Multiple OPA's to manage fistula's with multiple antibiotic treatments

co-trimoxazole and metronidazole 2nd trimester only

Dec 2014 – 35 weeks

Admitted with 2 collections Left labia and left thigh - syringe drainage with cold spray anaesthetic – options?

- Re-attended today for review of left groin + labial abscess, post needle aspiration 1/12/14.
- Labial abscess improved no fluctuance
- Groin abscess fluctuant 5x5cm - 12mls bloody pus aspirated.
- Low threshold for admission if becomes septic.

Dec 2014

Planned C - section

Mother and baby girl both doing well

In total

11 OPA with IBD team

1 ED visit

1 Inpatient stay

4 OPA with Maternal medicine

Who was involved?

IBD team – all of them

Maternal medicine team

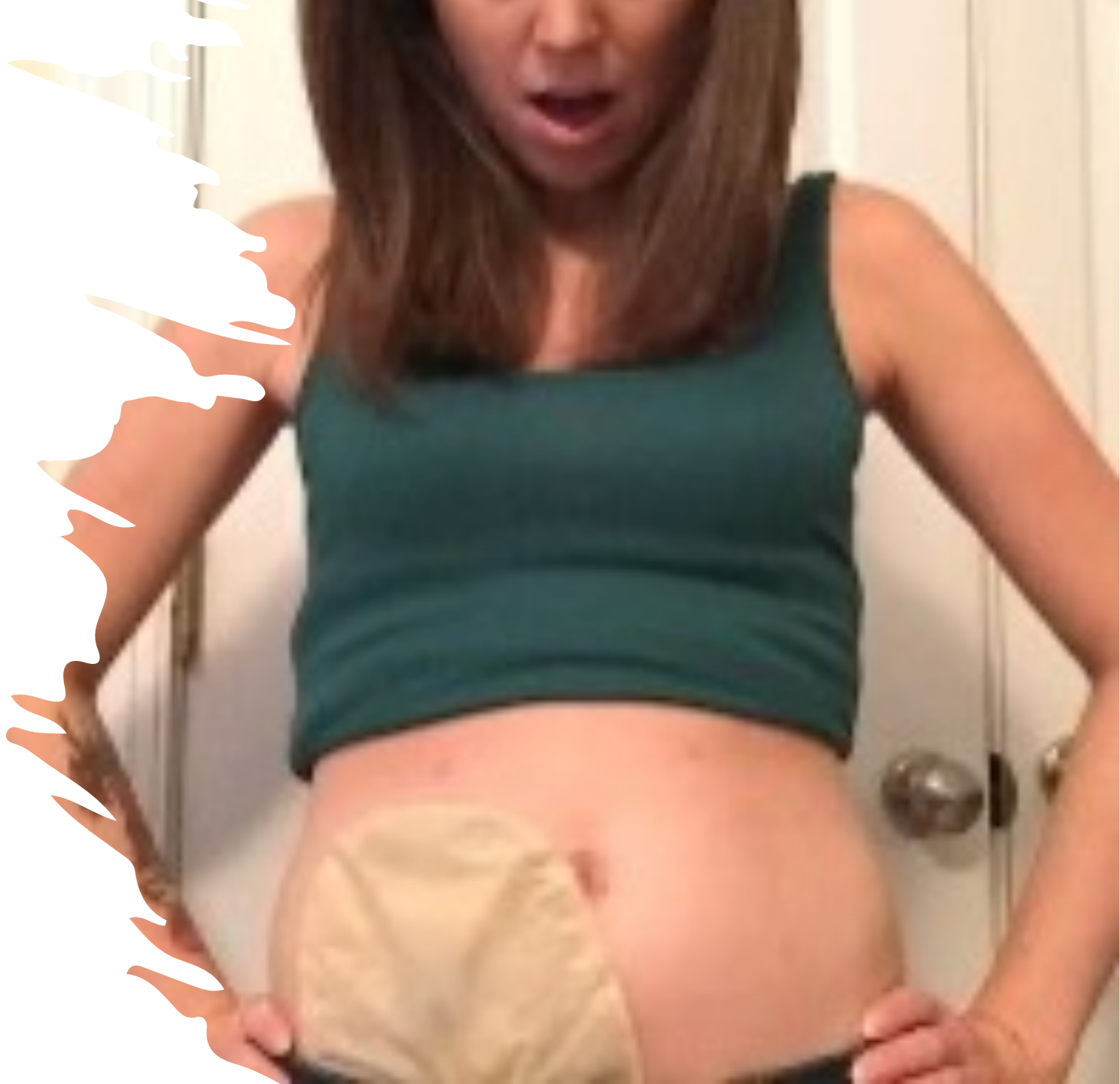
Colorectal surgeons

Microbiologist

Midwives

Radiologist

Monica



Monica 29 year old

- Complex colonic and small bowel Crohn’s
- First met having exhausted both anti-TNF’s
- Just married steroid dependent – Cushingoid
- Long admission PN, Vedo no response
- Total colectomy and end ileostomy

4 years later

- Transformed over the years
- Steroids all gone – required endocrine help
- Managed stoma well
- Fantastic support network – husband, family
- Back to work in the Police Force

Meets Dr Kok

- No one ever talked to me about children during my 4 month hospital stay…….
- I can’t have children I have a stoma?
- Won’t my kids get Crohn’s?

Syeda

Syeda 29 years old

Ileo-colonic Crohn’s disease

Diagnosed 10 years ago

No treatment for 6 years

Lost to follow up

Fertility

Had been trying to have children for 4 years

Commenced IVF

Success

Week 8 Flare – contacts IBD team via GP

Baby is scanned and is ok

Flare during pregnancy

Diarrhoea 5-6 times a day

Weight loss despite pregnancy

Postprandial abdominal pain

Hb 98 CRP 52

Alb 34 FCP 568

Now what?

Investigations

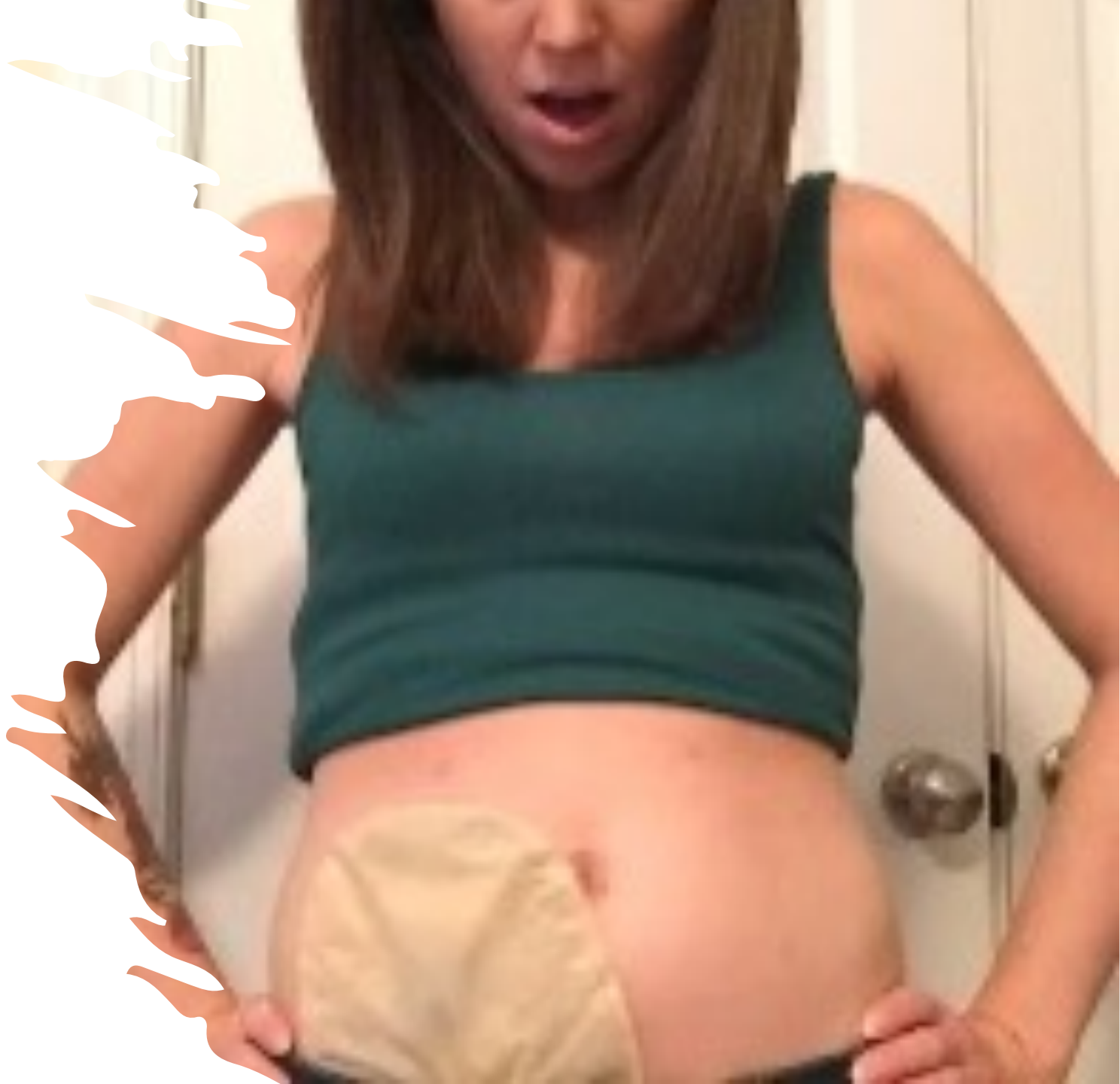
- MRI small bowel
  - Active ileal and caecal thickening
  - Skip lesion upstream
  - Trans mural disease with haziness in mesentery and reactive nodes

- Treatment Options
  - Steroids
  - Azathioprine
  - EEN
  - Anti-TNF

Outcome

- Rapid remission
- Continued anti-TNF throughout pregnancy
- Weight gain
- Healthy baby

Monica



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Question

Active inflammatory bowel disease during pregnancy

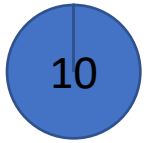
1 Does not affect the chance of having a healthy baby?

2 Does not cause early birth?

3 Should be put up with to protect the unborn from drug effects?

4 Should be treated with some types of drugs to protect the pregnancy?

Vote Now



Treat relapse as usual

Active disease highest risk for pregnancy > treat – similar as usual

- Anti-TNF for steroid refractory disease

- Thiopurine – avoid
  - Late disease response
  - Risk of bone marrow suppression
  - Risk pancreatitis

Most investigations are safe

- MRI safe
  - NOT gadolinium - stillbirth / neonatal death / childhood inflammatory dx

- Do lower GI endoscopy when strongly indicated regardless trimester
  - Diagnostic delay > treatment delay
  - Sigmoidoscopy safe throughout
  - Colonoscopy only if needed
  - Fentanyl and midazolam safe
    - Midazolam secreted in breast milk

Cappell et al. J Reprod Med 2010; Cappell et al., Dig Dis Sci 1996

Steroids

- 5 mg prednisolone per day for more than 3 weeks prior to delivery => parenteral steroids to cover the physiological stress of delivery
- Steroids in third trimester => fetal growth monitoring

Steroids

- Pregnancy - Increased plasma corticosteroids-binding globulin
- 11ß-hydroxysteroid dehydrogenase expressed in the placenta
- prednisolone inactivated by 11ß-HSD => fetal levels much lower than maternal levels
- dexamethasone, bethametasone, hydrocortisone cross the placenta

Ostensen Nat Rev Rheumatol 2009

Setting up an MDT clinic – Barts Health experience

- A lot of active disease
- A lot of fertility treatment
- Frequent start biologics

- Less NICU bed days
- Less appointments overall
- Less preterm birth
- Less low birth weight

- BSG guidance

Breastfeeding protective

- Breastfeeding confers a duration-dependent protection against the development of IBD

Crohn's disease	Ulcerative colitis
OR 0.45 (95% CI 0.26–0.79)	OR 0.56 (95% CI 0.38–0.81)

- Medications
- LACTMED

Royal College of
Obstetricians &
Gynaecologists

Coronavirus (COVID-19) Infection in Pregnancy

Information for healthcare professionals

Version 14: Published Wednesday 25 August

Royal College of Obstetricians & Gynaecologists | THE ROYAL COLLEGE OF MIDWIVES | uktis uk teratology information service | MOMS MacDonald Obstetric Medicine Society

Information sheet and decision aid: Updated 20 August 2021

All pregnant women in the UK over the age of 18 have now been offered COVID-19 vaccination. Pregnant women aged 16 and 17 will be offered a COVID-19 vaccine this summer.

Vaccination is recommended in pregnancy, but the decision whether to have the vaccine is your choice. The information below will help you make an informed choice about whether to get the COVID-19 vaccine if you are pregnant or trying to get pregnant.

Your options:

 **Get a COVID-19 vaccine** **or**  **Wait for more information about the vaccine in pregnancy**

What are the benefits of the vaccination?

✓ **COVID-19 may be more dangerous in pregnancy**

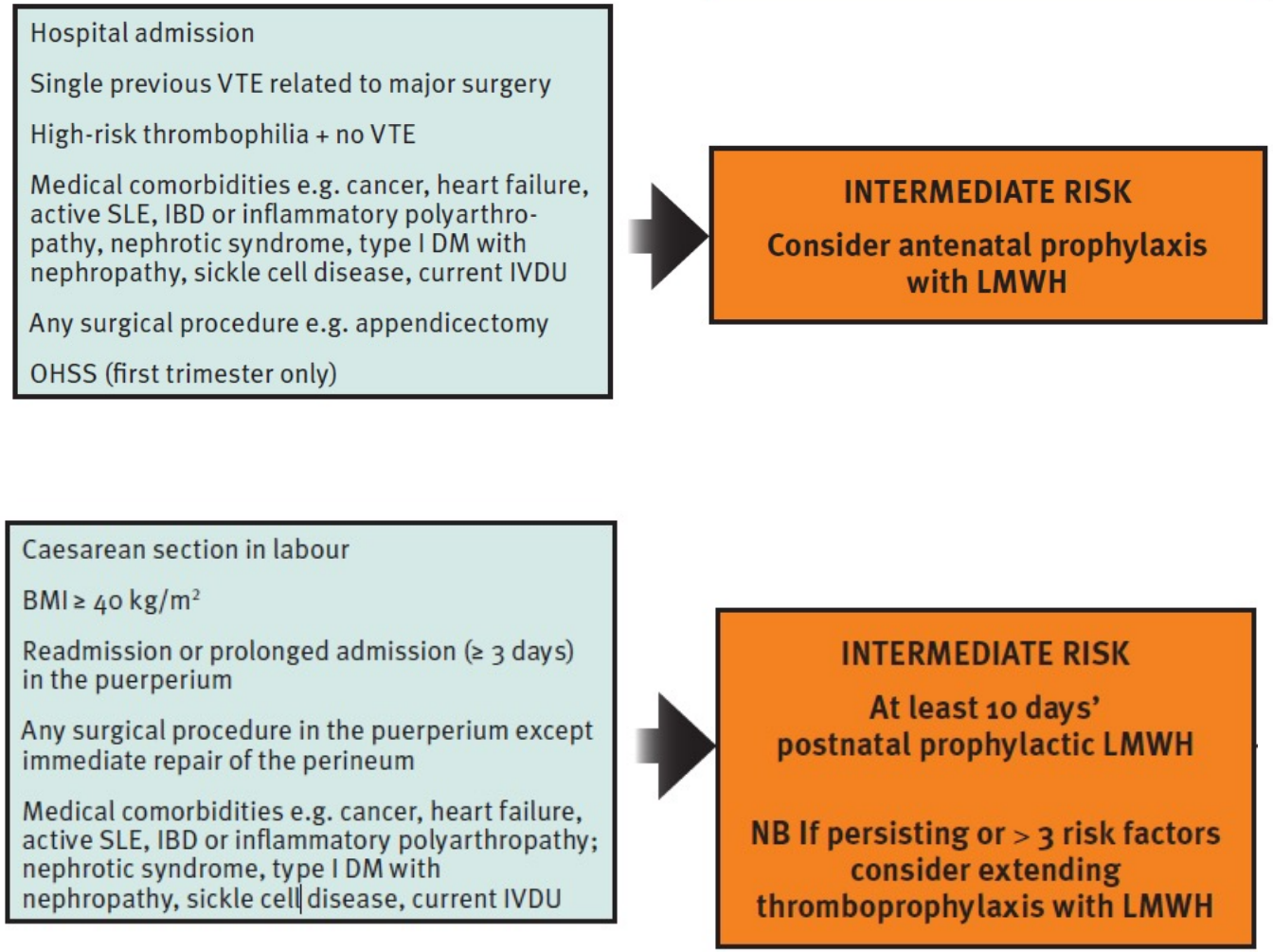
Studies have shown that hospital admission and severe illness are more common in pregnant women (compared to those not pregnant), especially those in the third trimester of pregnancy, and that stillbirth and preterm birth is more likely (compared to pregnant women without COVID-19). Pregnant women with underlying medical conditions are at higher risk of severe illness.

✓ **Vaccination is effective in preventing COVID-19 infection**

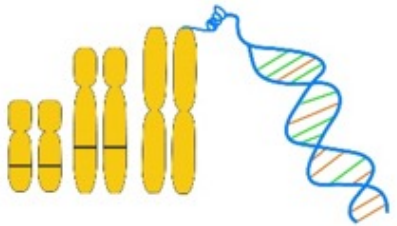
✓ **You cannot get COVID-19 from vaccination**

- COVID-19 vaccines do NOT contain live coronavirus
- Vaccines do NOT contain any additional ingredients that are harmful to pregnant women or their babies
- Other non-live vaccines (whooping cough, influenza) are safe for pregnant women and their unborn babies.

VTE – active IBD = risk

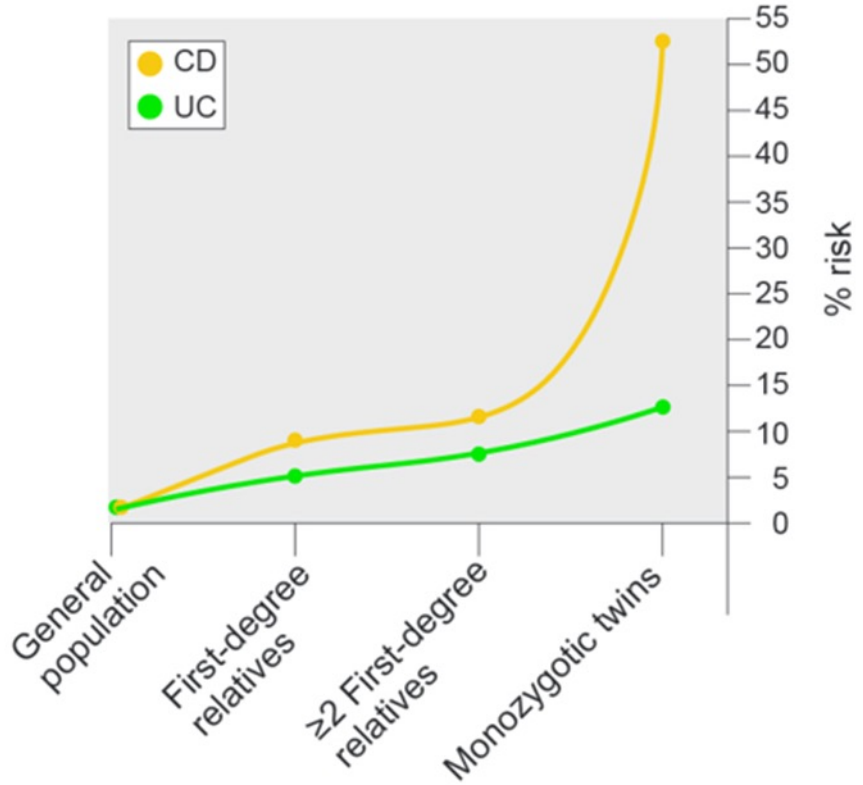


Genetic risk



Often overestimated

- 10% of IBD patients have family member with IBD
- Maternal CD - **absolute** risk of an offspring developing CD is 2.7%
- Maternal UC - **absolute** risk of an offspring developing UC is 1.6%

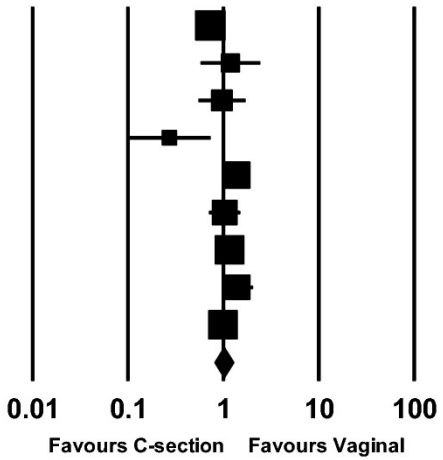


Trends for familial risk of IBD, based on data from an population-based cohort study

Risk OFFSPRING

odds of IBD in individuals born by C-section compared to vaginal delivery.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bager 2012	0.730	0.680	0.784	-8.657	0.000
Black 2015	1.186	0.581	2.423	0.468	0.639
Roberts 2011	0.966	0.550	1.700	-0.118	0.906
Bengtson 2010	0.272	0.101	0.733	-2.575	0.010
Ponsonby 2009	1.380	1.044	1.825	2.261	0.024
Hutfless 2012	1.032	0.710	1.500	0.163	0.870
Malmborg 2012	1.159	0.993	1.352	1.874	0.061
Sonntag 2007	1.407	0.974	2.034	1.817	0.069
Bernstein 2015	0.992	0.845	1.166	-0.094	0.925
	1.012	0.808	1.267	0.103	0.918

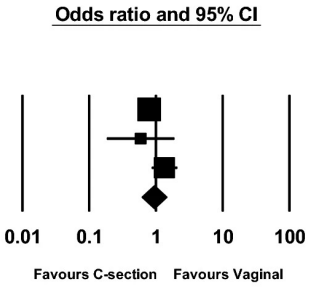


Meta Analysis

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Kristensen 2016	0.764	0.551	1.060	-1.610	0.107
Roberts 2011	1.194	0.624	2.285	0.535	0.593
Ponsonby 2009	1.380	1.044	1.825	2.261	0.024
Malmborg 2012	1.159	0.993	1.352	1.874	0.061
Sonntag 2007	1.451	0.975	2.161	1.833	0.067
	1.154	0.936	1.423	1.343	0.179

Meta Analysis

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Kristensen 2016	0.794	0.590	1.069	-1.521	0.128
Roberts 2011	0.591	0.186	1.883	-0.889	0.374
Sonntag 2007	1.344	0.870	2.077	1.331	0.183
	0.943	0.612	1.453	-0.267	0.790

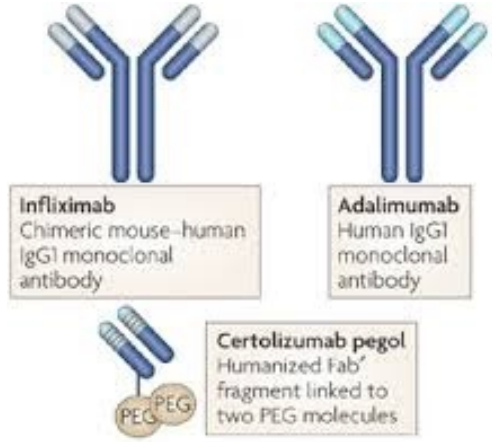


Meta Analysis

Frias Gomes C, et al. Dig Dis Sci. 2021 Feb;66(2):398-407

vaccination

Rotavirus	8 weeks, 12 weeks
MMR vaccine	1 year, 3 years
Nasal flu vaccine	2 years up to school year 5
Shingles vaccine	70+
Chickenpox	Not routinely given
BCG	4 weeks, high risk areas
Yellow Fever	(travel vaccine only)
Oral typhoid	(travel vaccine only)
(oral polio)	3 year

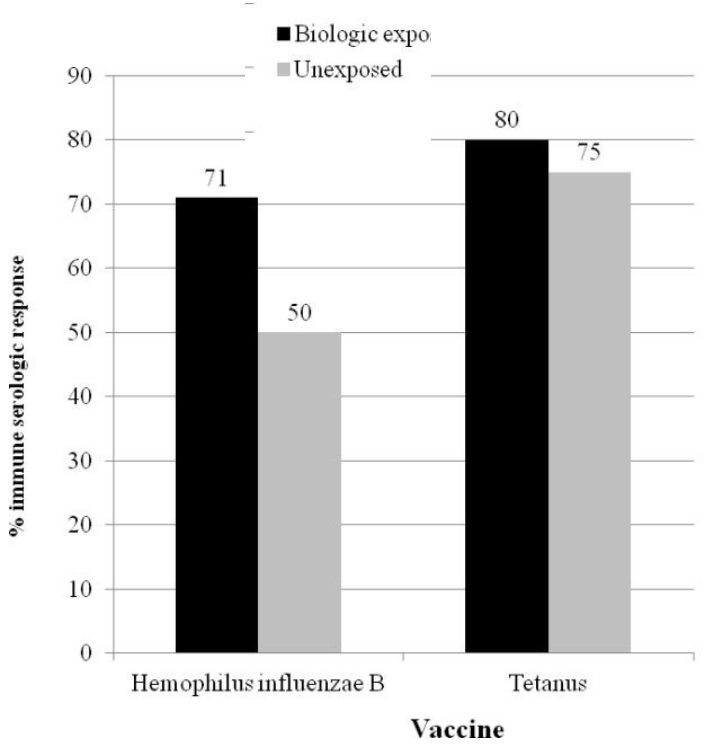


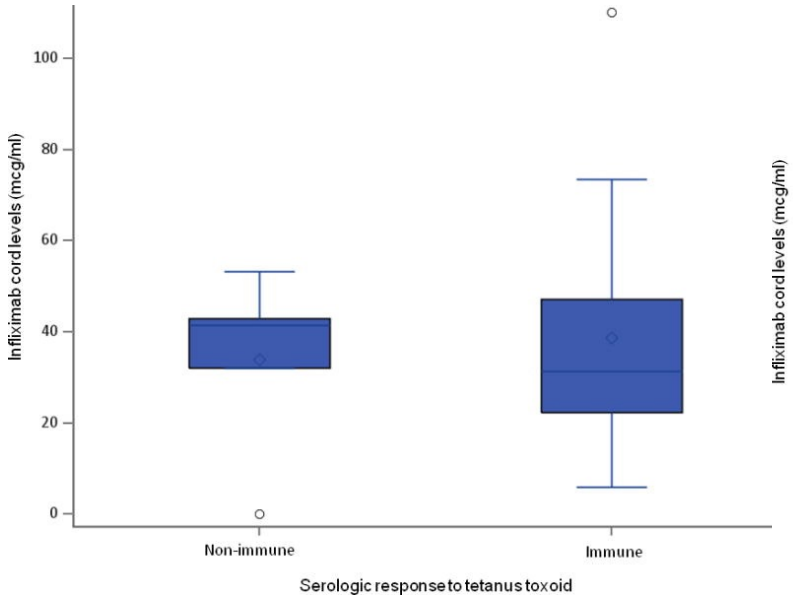
Vaccination[88]

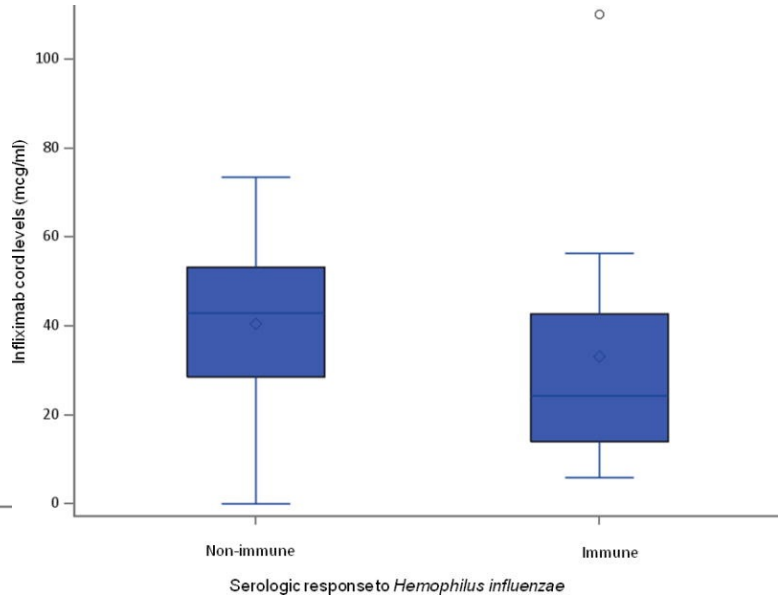
- Numerous studies have assessed whether vaccines may be linked to the development of IBD
  - Multiple vaccines and timings
  - Multiple study types
    - Case–control
    - Prospective long-term case–cohort
    - Inception cohort
    - Meta-analyses

There is no association between childhood vaccinations and the later development of IBD

Vaccination efficacy newborn not affected by biologics

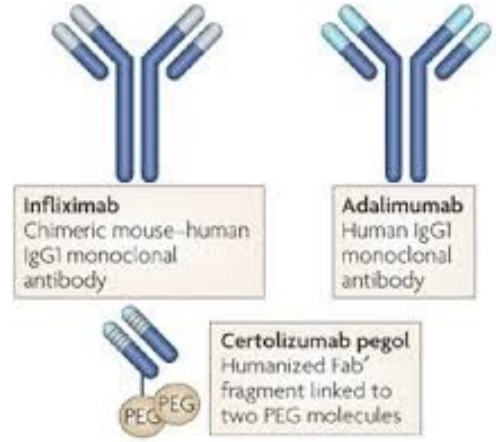






Beaulieu DB, et al. Clin Gastroenterol Hepatol. 2018 Jan;16(1):99-105

Anti-TNFs / biologics



- IgG1 – cross placenta
  - aTNF cord > maternal levels (IFX > ADA)
- Safe – pregnancy and neonate
  - non-serious neonatal infections aTNF/thiopurine
  - No long-term child studies
- Higher relapse rates when aTNF stopped
  - 36-39% vs. 25-26%
- Live vaccines not safe for 6 months (all biologics)

Guidance on biologics

ECCO (2015) (remission) stop – week 24-26

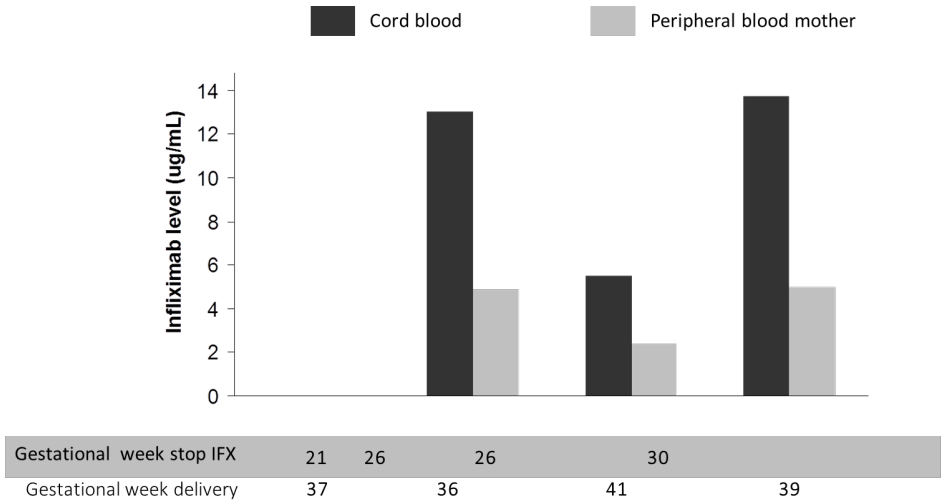
TORONTO (2016) only stop if low risk relapse

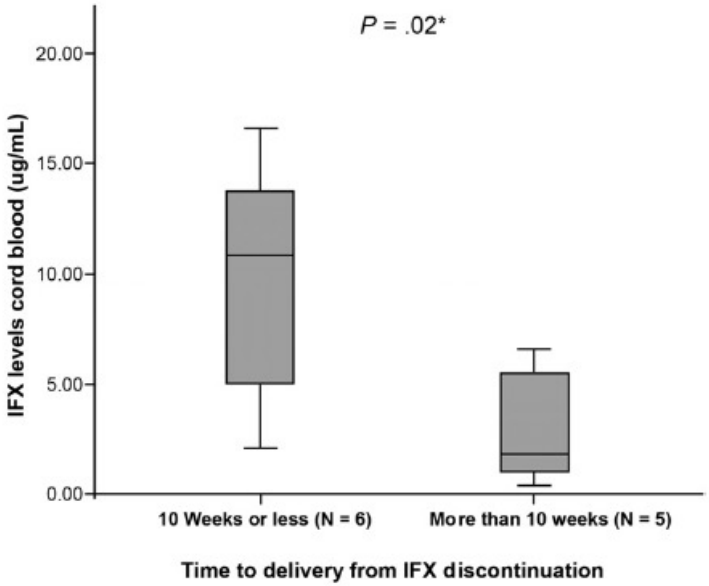
AGA (2019)

– continue all biologics

- Last IFX 6-10 weeks before EDD
- Last ADA 2-3 weeks (1-2 for weekly)
- Golimumab 4-6 weeks
- Last VED 6-10 weeks (4-5 for 4-weekly)
- Last UST 6-10 weeks

Placental transfer anti-TNF levels

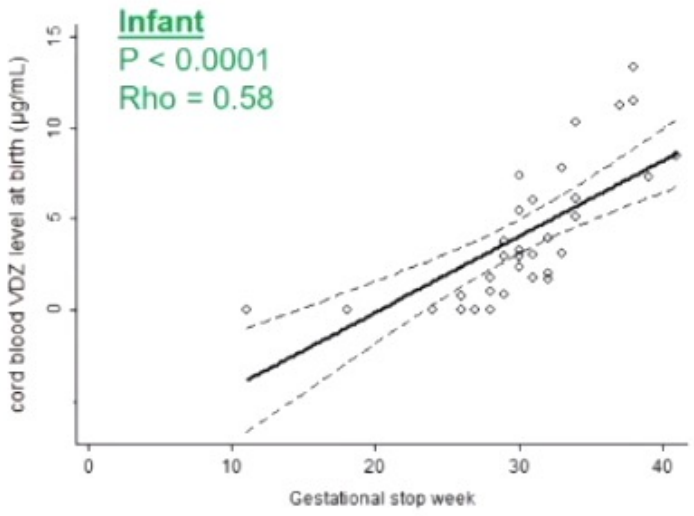


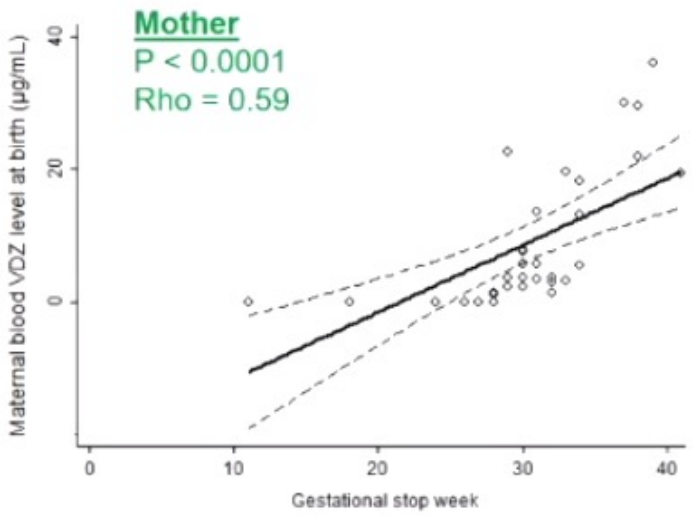


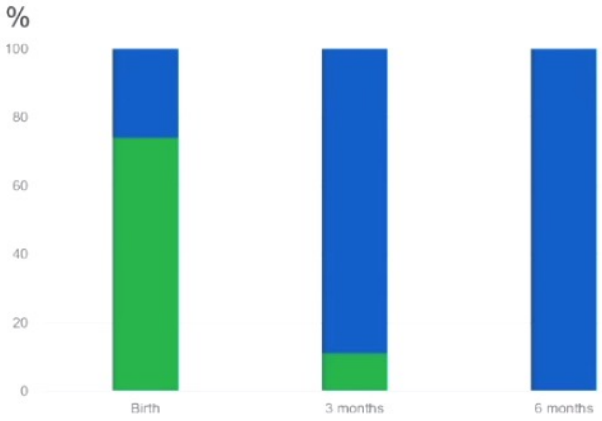
Zelinkova et al, Aliment Pharmacol Ther 2011; Zelinkova et al, Clin Gastroenterol Hepatol 2012

Vedolizumab

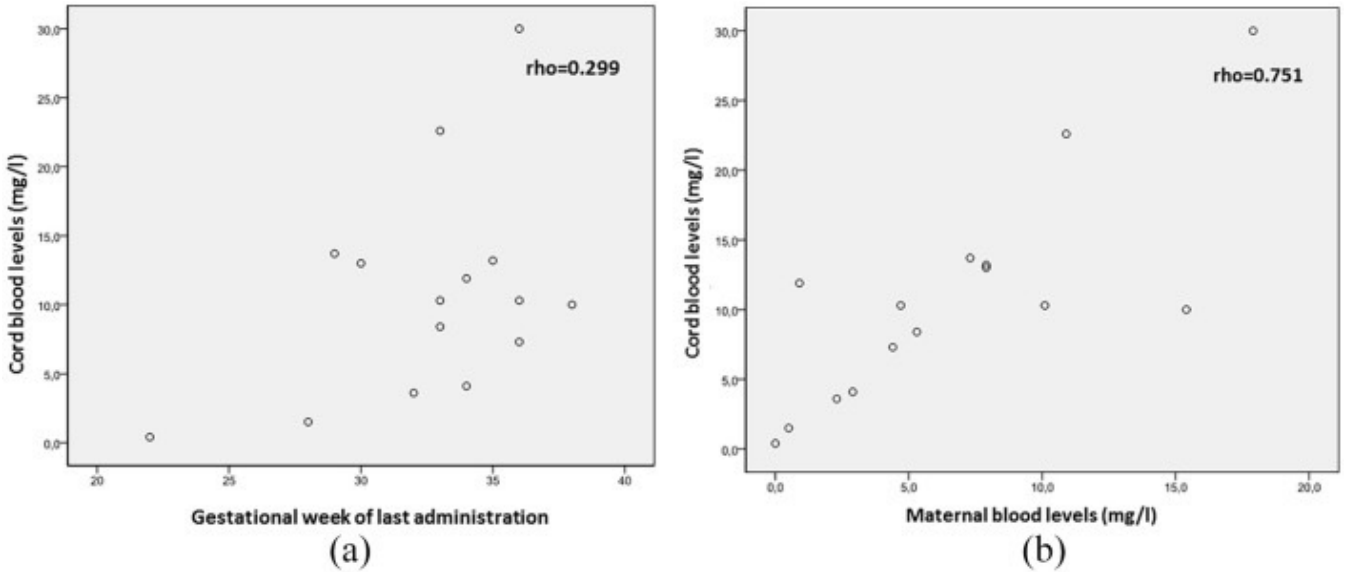
- Cord levels lower than maternal levels
- Quick infant vedolizumab clearance
  - Not influenced by birth weight or breastfeeding







Ustekinumab



Mitrova K, et al. Therap Adv Gastroenterol. 2021 Aug 7;14

Ustekinumab

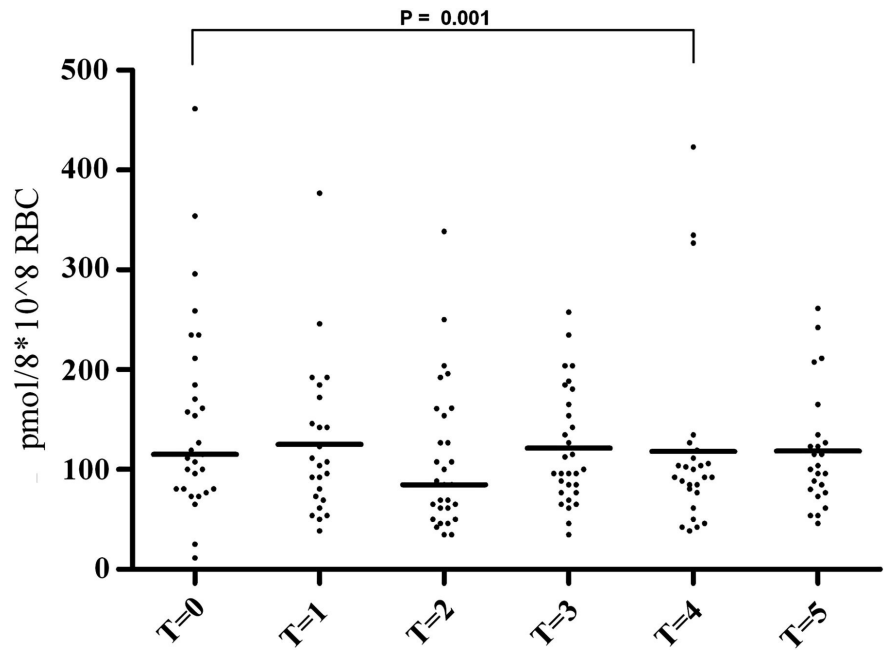
- Safe in animal studies
- 26 maternal exposures in the Crohn’s disease clinical trials programme, drug stopped when pregnancy confirmed - nil adverse reported

These data do not allow for general recommendations

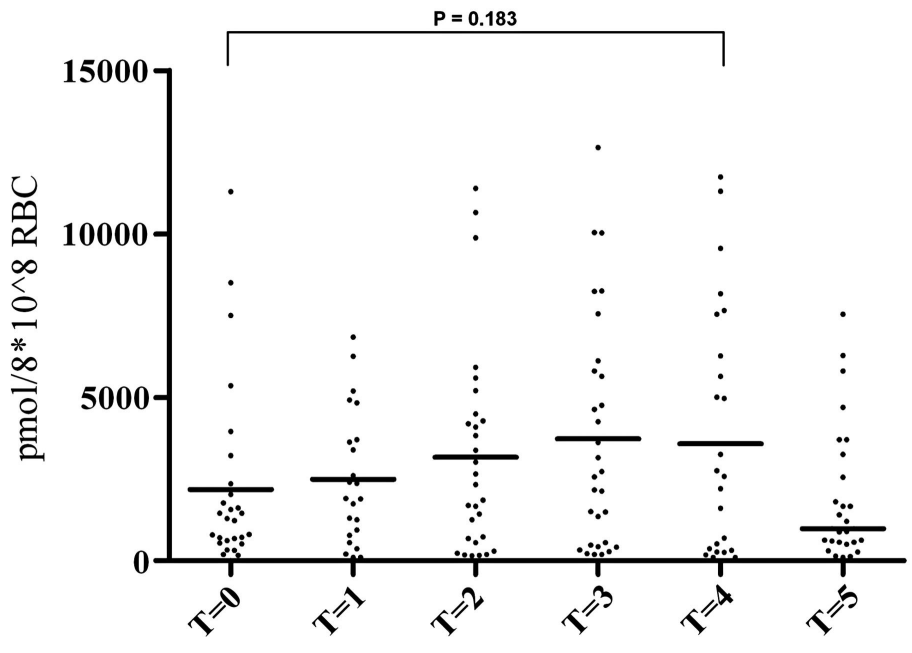
advice for any individual patient needs to carefully consider potential risks and benefits

Thiopurine metabolites

TGN



MMP



T=0, before conception; T=1, directly after pregnancy confirmation; T=2, after the first trimester; T=3, after the second trimester; T=4, delivery; T=5, 3 months after delivery

Jharap B, et al. Gut. 2014 Mar;63(3):451-7

• Sulfasalazine • Mesalazine	• Azathioprine • 6-Mercaptopurine • Methotrexate • Tofacitinib • Allopurinol	• Infliximab • Adalimumab • Vedolizumab • Ustekinumab	• Budesonide • Prednisolone • Hydrocortisone • Tacrolimus • Ciclosporin	• Ciprofloxacin • Metronidazole • Movicol • Loperamide • Codeine • Omeprazole • Lansoprazole

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Bethesda (MD): National Library of Medicine (US); 2006-.

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