INFECTIONS AND CANCER IN IBD

Minimising risks during pregnancy

Fabiana Castiglione
"Federico II" University of Naples

Inflammatory bowel disease and pregnancy: Lack of knowledge is associated with negative views

Christian P. Selinger [a, b, *], Jayne Eaden [c], Warwick Selby [d], D. Brian Jones [a], Peter Katelaris [a], Grace Chapman [a], Charles McDondald [a], John McLaughlin [b], Rupert W.L. Leong [a, e], Simon Lal [b]

145 participants

- **24% felt it more important to tolerate symptoms**
- **36% believed that all IBD medication is harmful to unborn children**
- **68% agreed with need for medical therapy for flares**

The correlation between knowledge and attitudes towards medication use during pregnancy appears therefore strong.

Journal of Crohn's and Colitis 2013

Minimising risk in pregnancy: CONCLUSIONS

..... pregnant patients and their primary physicians, gastroenterologists and obstetricians must all be educated to the fact that the greatest risk to pregnancy is active disease, not active treatment.

D. Sachar

ECCO Guidelines/Consensus Paper

The Second European Evidenced-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease

C.J. van der Woude,[a*†] S. Ardizzone,[b] M.B. Bengtson,[c] G. Fiorino,[d] G. Fraser,[e] K. Katsanos,[f] S. Kolacek,[g] P. Juillerat,[h] A.G.M.G.J. Mulders,[i] N. Pedersen,[j] C. Selinger,[k] S. Sebastian,[l] A. Sturm,[m] Z. Zelinkova,[n] F. Magro,[o,p,q†] for the European Crohn's and Colitis Organization (ECCO)

Minimising risks in pregnancy: counseling prior conception

ECCO Statement 5F

Discontinuation of maintenance therapy may result in disease relapse and appropriate counseling of the patient, ideally prior conception, is helpful in preventing non adherence to the treatment due to fear of potential harm to the unborn child [EL5]

Journal of Crohn's and Colitis 2015

WHAT IS A ”SAFE” DRUG IN PREGNANCY?

- **In the mother:**
  – No additional side effects compared to non-pregnant patients

- **For pregnancy:**
  – No induction of pregnancy complications like miscarriage or prematurity

- **In the child:**
  – No short term or longterm adverse effects

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Special Article

Safety of treatments for inflammatory bowel disease: Clinical practice guidelines of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

Category A	Adequate research has been done with the conclusion that drugs in this category are not likely to cause any harm to the fetus in the first trimester as well as later in pregnancy.	
Category B	Studies carried out on animals have shown no adverse effects on the fetus; however, there is a lack of controlled studies on human pregnancy.	Mesalazine Sulfasalazine Balsalazide Metronidazole Infliximab Adalimumab Golimumab Vedolizumab
Category C	Animal studies have shown evidence of harmful effects on the fetus; however, no controlled study has been done on a human pregnancy. The medicines may be prescribed in cases where the potential benefits outweigh the possible adverse effects.	Olsalazine Systemic corticosteroids Budesonide Beclomethasone dipropionate Ciprofloxacin Rifaximin Cyclosporine
Category D	Studies done on human pregnancy have shown positive risks to the fetus. However, doctors might prescribe them in certain cases where the potential benefits outweigh the risks.	Azathioprine 6-mercaptopurine
Category X	Both human and animal studies have shown positive risks to the fetus, with the adverse effects extending to serious birth defects, miscarriage and fetal death. The possible risks of using these medicines outweigh any potential benefits.	Methotrexate

Biancone L, Dig Liver Dis 2017

CHANGES IN PHARMACOKINETICS DURING PREGNANCY

Absorption
- Reduction of intestinal motility
- Increased gastric pH

Distribution
- Increased volume distribution
- Decreased albumin (2^- 3^ trimester)

Impact on the elimination half-life

Metabolism
- **Mother**

o Changes in CYP, UGT, NAT expression
o Increased liver blood flow

Placenta and child
- Passive transport
- Transporters 'in&out'
- Immunoglobulins transfer

Renal excretion
- Increased glomerular filtration
- Changes in tubular excretion and reabsorption

Anderson GD, Clin Pharmacokinet 2005

SAFETY OF IMMUNOSUPPRESSIVE THERAPY IN PREGNANCY

- Steroids
- Thiopurines
- Cyclosporine

- Anti TNF-a agents
  - Infliximab
  - Adalimumab
  - Golimumab

- Vedolizumab
- Ustekinumab

SAFETY OF IMMUNOSUPPRESSIVE THERAPY IN PREGNANCY

- Steroids
- Thiopurines
- Cyclosporine

- Anti TNF-a agents
  - Infliximab
  - Adalimumab
  - Golimumab

- Vedolizumab
- Ustekinumab

Systemic and low bioavailability corticosteroids (FDA Class C)

•All corticosteroids can cross the placenta, but are converted to less active metabolites by placental enzymes → **low fetal blood concentration**

•**Prednisone, prednisolone, and methylprednisolone** (short-acting steroids) are the **preferred agents** during pregnancy

•A few studies have reported the safety of **budesonide** and **BDP** in pregnancy or breastfeeding in IBD pts

Hviid A, CMAJ 2011
Beaulieu DB, Inflamm Bowel Dis 2009

Corticosteroids: risk of congenital malformations or defects in the palate

	No use of inhaled or oral corticosteroids at any time during pregnancy	Use of inhaled or oral corticosteroids in early pregnancy	Use of inhaled corticosteroids in early pregnancy	Use of oral corticosteroids in early pregnancy
Number of women	80,950	1449	1223	226
Congenital malformations				
Number	3446	63	53	10
Prevalence (%)	4.3	4.3	4.3	4.4
POR (95% CI)	Reference	1.02 (0.79–1.32)	1.02 (0.77–1.34)	1.04 (0.55–1.96)
Oral clefts				
Number	145	1	1	0
Prevalence (%)	0.2	0.07	0.08	—
POR (95% CI)	Reference	0.39 (0.05–2.75)	0.47 (0.07–3.34)	—

Bay Bjorn AM, Am J Ther 2014

Corticosteroids (FDA Class C)

- corticosteroids do transfer to the breast milk, but in very low levels (0.1% of maternal dose)

- the highest levels appear in the first 4 hrs

"Lactation" is recommended 4 hrs after steroids consumption to minimize transfer of the drug to the neonate (if dose > 20 mg/day)

Corticosteroids can be continued during pregnancy and lactation

Nielsen OH, Nat Rev Gastroenterol Hepatol 2014
Greenberger PA, Clin Pharmacol Ther 1993

SAFETY OF IMMUNOSUPPRESSIVE THERAPY IN PREGNANCY

- Steroids
- Thiopurines
- Cyclosporine

- Anti TNF-a agents
  - Infliximab
  - Adalimumab
  - Golimumab

- Vedolizumab
- Ustekinumab

Thiopurines (FDA class D)

In animals

○ increased risk for several malformations

The doses used and the route of delivery (intraperitoneal, subcutaneous) produce much higher drug concentrations than used in humans

Placental concentration of AZA:

-from 64 to 93% of the maternal blood level

The placenta forms a barrier to AZA and its metabolites

Concentration in foetal blood:

- only 1–5% of their respective maternal blood levels

Matalon ST, Reproductive Toxicology 2004

Polifka JE, Teratology2002

Pregnancy outcome in patients with inflammatory bowel disease treated with thiopurines: cohort from the CESAME Study

Jessica Coelho,[1] Laurent Beaugerie,[2] Jean Frédéric Colombel,[3] Xavier Hébuterne,[4] Eric Lerebours,[5] Marc Lémann,[6] Philippe Baumer,[2] Jacques Cosnes,[2] Arnaud Bourreille,[7] Jean Pierre Gendre,[2] Philippe Seksik,[2] Antoine Blain,[2] Etienne H Metman,[8] Andrée Nisard,[1] Guillaume Cadiot,[9] Michel Veyrac,[10] Benoît Coffin,[11] Xavier Dray,[1] Fabrice Carrat,[12] Philippe Marteau,[1] for the CESAME pregnancy study group (France)

Cohort study including 84 pregnancies in IBD pts and 129 controls

Table 3 Pregnancy and fetal outcomes according to drug exposure groups

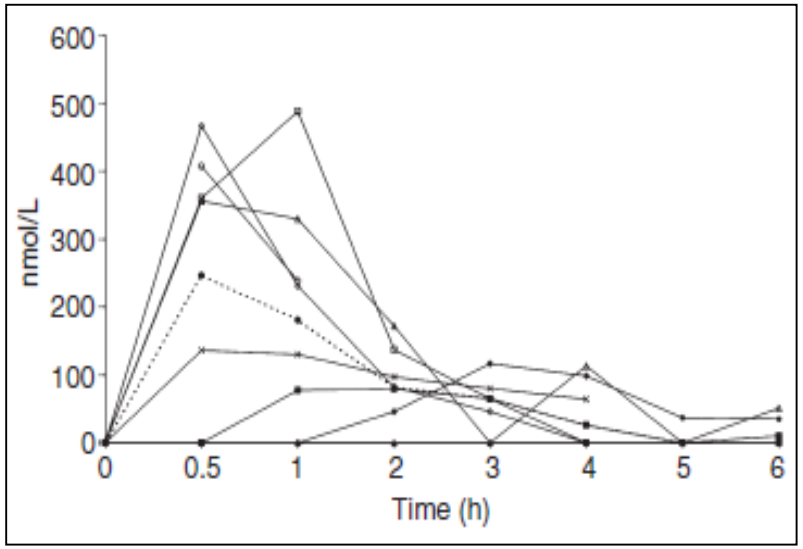
Outcome	Group A (n=86)	Group B (n=84)	Group C (n=45)	p Value
Live births*	64.0% (53.9% to 74.1%)	66.6% (56.5% to 76.7%)	60.0% (45.7% to 74.3%)	NS‡
Prematurity*	21.8% (10.9% to 32.7%)	16.0% (6.4% to 25.6%)	14.8% (1.4% to 28.2%)	NS§
Birth weight†	3114±654 (1495–4500)	3088±645 (1250–4150)	3289±465 (2300–4070)	NS§
Low birth weight <2500 g*	15.8% (6.3% to 25.3%)	13.8% (5.0% to 22.6%)	7.4% (0.0% to 17.3%)	NS§
No. of congenital abnormalities*	2 3.6% (0.0% to 8.5%)	4 7.1% (0.5% to 13.7%)	0 0.0% (0.0% to 0.0%)	NS§

Group A, women exposed to thiopurines; Group B, women receiving a drug other than thiopurines; Group C, women receiving no medication.

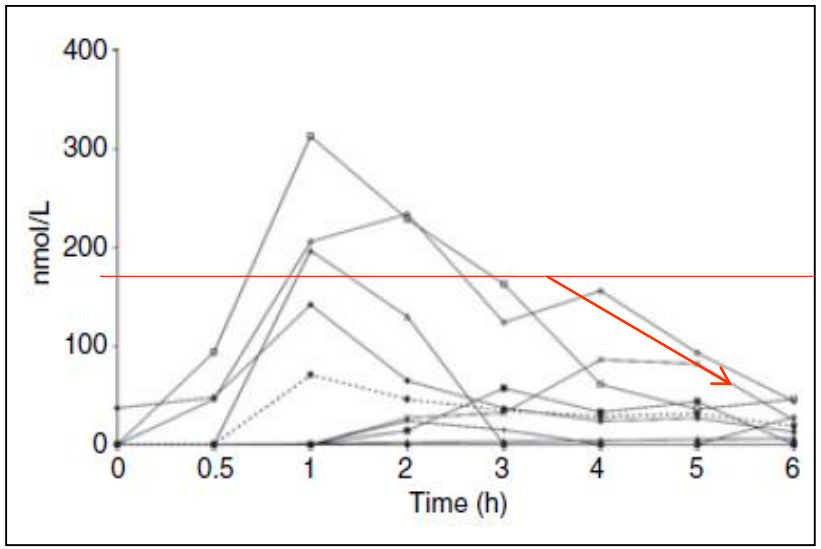
Gut 2011

Azathioprine treatment during lactation

L. A. CHRISTENSEN*, J. F. DAHLERUP*, M. J. NIELSEN*, J. F. FALLINGBORG† & K. SCHMIEGELOW‡



6-MP concentrations in maternal plasma



6-MP concentrations in maternal milk

Azathioprine and 6-MP can be continued during breastfeeding "Lactation" is recommended 4 hrs after drug consumption to minimize the transfer to the neonate

Aliment Pharmacol Ther 2008

Long-term follow-up of children exposed intrauterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease

T. G. J. de Meij*, B. Jharap†, C. M. F. Kneepkens*, A. A. van Bodegraven† & N. K. H. de Boer† for the Dutch Initiative on Crohn and Colitis[1]

Prospective multicentre follow-up study

30 exposed children [median 3.8 years (IQR 2.9–4.7)]- Control group: 340 children

- physical, cognitive and social aspects of infant health status → assessed with the TNO-AZL Preschool Children Quality of Life Questionnaire (TAPQOL)

Thiopurine use during pregnancy did not affect long-term development or immune function of children up to 6 years of age

✓no statistically significant differences between the breastfed and formula-fed children with regard to TAPQOL scores in any of the 12 domains

Aliment Pharmacol Ther 2013

Use of Thiopurines During Conception and Pregnancy not Associated With Adverse Pregancy Outcomes or Health of Infants at 1 Year in a Prospective Study

Table 5. One-year health outcomes of infants: univariate and multivariate logistic regression analysis						
	Study group (n=83)	Control group (n=141)	*P* value	Crude OR (95%CI)	Adjusted OR (95%CI)	*P* value
Growth deficiency (%)	2 (2.4)	4 (2.8)	1.00	-	-	-
Infection (yes/no) (%)	27 (33.8)	44 (31.7)	.77	1.03 (0.58-1.85)	1.02 (0.57-1.83)a	1.00
Number of infections (%)						
0	53 (66.2)	89 (64.0)	.77	1.10 (0.62-1.97)	1.12 (0.63-1.99)a	.71
1-2	24 (30.0)	41 (29.5)	1.00	1.02 (0.56-1.87)	1.01(0.55-1.85)a	.97
≥ 3	3 (3.8)	9 (6.5)	.54	0.56 (0.15-2.14)	-	.40
Hospitalization because of an infection (%)	8 (9.9)	10 (7.2)	.61	1.28 (0.49-3.31)	1.30 (0.50-3.28)a	.60
Allergies (%)	10 (12.0)	10 (7.1)	.20	1.83 (0.73-4.61)	1.72 (0.67-4.38)b	.25
Adverse reaction(s) to vaccination(s) (%)	0 (0.0)	1 (0.7)	1.00	-	-	-
Eczema (%)	13 (18.3)	22 (18.3)	1.00	1.00 (0.47-2.13)	0.98 (0.45-2.13)c	.95

Kanis S L, Clin Gastroenterol Hepatol 2017

SAFETY OF IMMUNOSUPPRESSIVE THERAPY IN PREGNANCY

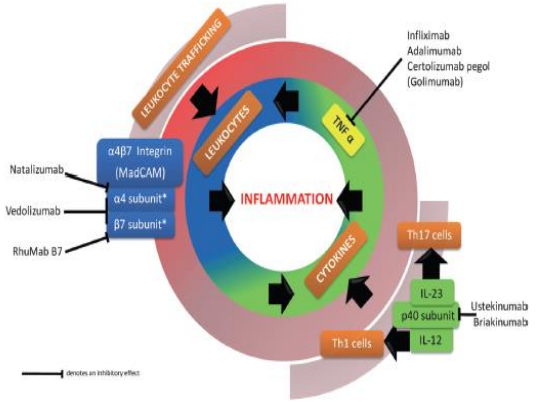
- Steroids
- Thiopurines

Anti TNF-a agents

Infliximab

Adalimumab

Golimumab



- Vedolizumab
- Ustekinumab

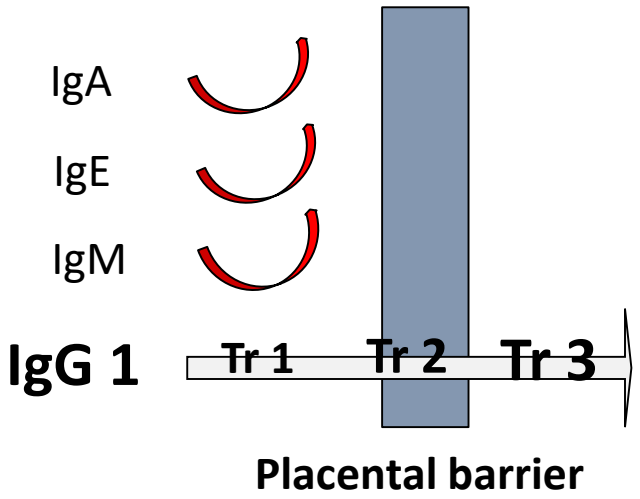
Anti TNF-a (FDA class B)

- Infliximab
- Adalimumab
- Golimumab

} IgG1 monoclonal antibodies

Human placenta: impermeable to all except IgG

Ig require **active transport** (using a specific neonatal Fc receptor on the placenta)



IgG: transfer occurs mainly during the third trimester

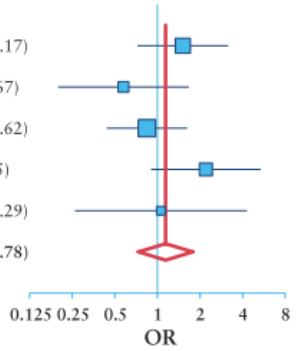
Brandtzaeg P, J Pediatr 2010

Anti-Tumour Necrosis Factor α Therapies and Inflammatory Bowel Disease Pregnancy Outcomes: A Meta-analysis

Zaid Shihab,[a] Neville D. Yeomans,[a,b] Peter De Cruz[a–e]

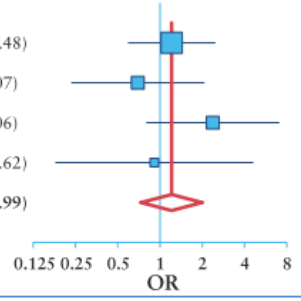
Adverse Pregnancy Outcomes

Author	anti-TNFα	Disease Controls	OR (CI)
Seirafi[46]	24 (118)	13 (90)	1.51 (0.72; 3.17)
Lichtenstein[47]	6 (80)	10 (81)	0.58 (0.2; 1.67)
Casanova[48]	14 (60)	74 (279)	0.84 (0.44; 1.62)
Schnitzler[50]	14 (32)	17 (65)	2.2 (0.9; 5.35)
Johnson[51]	27 (95)	3 (11)	1.06 (0.26; 4.29)
Synthesis	**85 (385)**	**117 (526)**	**1.14 (0.73; 1.78)**



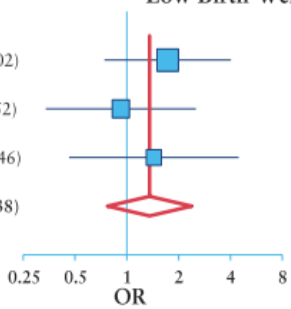
Preterm Birth

Author	anti-TNFα	Disease Controls	OR (CI)
Seirafi[46]	23 (118)	15 (90)	1.21 (0.59; 2.48)
Casanova[48]	4 (60)	26 (279)	0.7 (0.23; 2.07)
Schnitzler[50]	8 (32)	8 (65)	2.38 (0.8; 7.06)
Johnson[51]	16 (95)	2 (11)	0.91 (0.18; 4.62)
Synthesis	**51 (305)**	**51 (445)**	**1.21 (0.73; 1.99)**



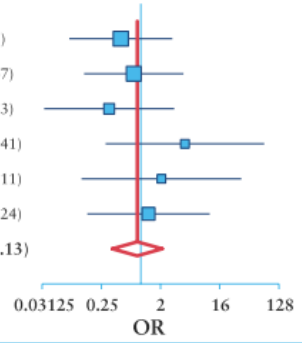
Low Birth Weight

Author	anti-TNFα	Disease Controls	OR (CI)
Seirafi[46]	19 (118)	9 (90)	1.73 (0.74; 4.02)
Casanova[48]	5 (60)	25 (279)	0.92 (0.34; 2.52)
Schnitzler[50]	6 (32)	9 (65)	1.44 (0.46; 4.46)
Synthesis	**30 (210)**	**43 (434)**	**1.36 (0.77; 2.38)**



Congenital Abnormalities

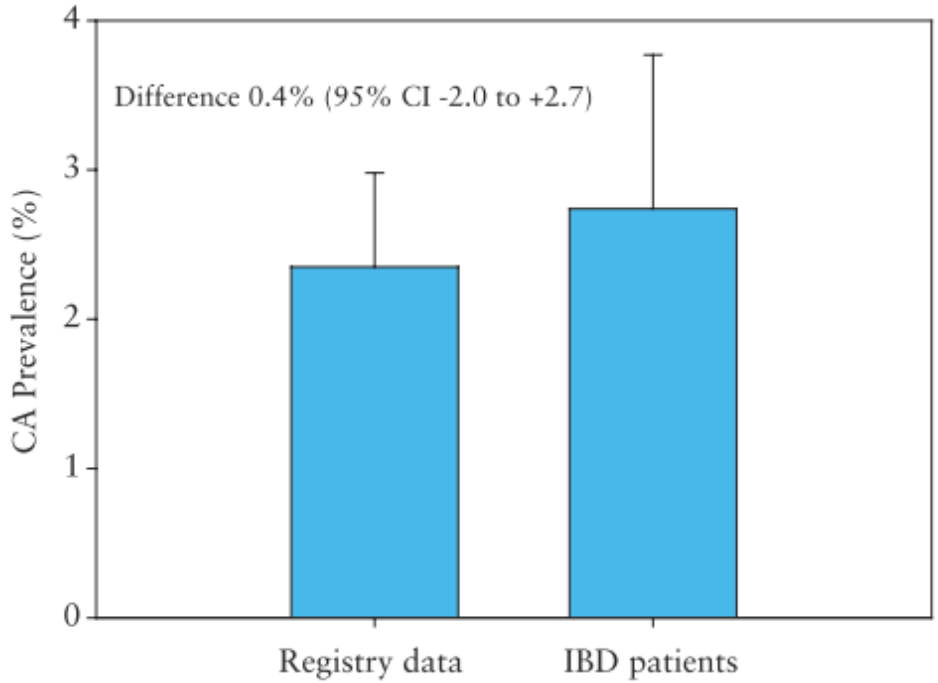
Author	anti-TNFα	Disease Controls	OR (CI)
Seirafi[46]	2 (119)	3 (90)	0.5 (0.08; 3.03)
Diav-Citrin[91]	2 (41)	4 (65)	0.78 (0.14; 4.47)
Lichtenstein[47]	1 (80)	3 (81)	0.33 (0.03; 3.23)
Casanova[48]	1 (60)	1 (279)	4.71 (0.29; 76.41)
Schnitzler[50]	1 (32)	1 (65)	2.06 (0.12; 34.11)
Johnson[51]	11 (95)	1 (11)	1.31 (0.15; 11.24)
Synthesis	**18 (427)**	**13 (591)**	**0.89 (0.37; 2.13)**



Journal of Crohn's and Colitis 2016

Anti-Tumour Necrosis Factor α Therapies and Inflammatory Bowel Disease Pregnancy Outcomes: A Meta-analysis

Zaid Shihab,[a] Neville D. Yeomans,[a,b] Peter De Cruz[a–e]



The risk of congenital abnormalities (CA) is not increased when prevalence data are compared with data for the general population

Journal of Crohn's and Colitis 2016

PIANO: A 1,000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy.

Unexposed	326
Goup A AZA, 6-MP	204
Group B Biologics	291
GroupAB Combo Tx	75
Babies n. total	896

Biologics used:
IFX, ADA, CZP, natalizumab

CD 57%, UC 43%

- **No increase in congenital anomalies**
- **No increased risk for neonatal infections** in any of the treatment groups overall

Group B: increase in spontaneous abortion (RR 2.56) and cesarean section (RR 1.23)

Group AB: more frequent preterm birth

Analysis without patients receiving CZP:
a 35% increase in (minor) infections by month 12 in infants exposed to **combotherapy** (RR 1.35, 95% CI 1.01 to1.80) compared to infants exposed to monotherapy.

Drug exposure did not appear to be associated with any differences in developmental milestones at months 4, 9, or 12.

Mahadevan U, DDW 2012; 865

Concentrations of Adalimumab and Infliximab in Mothers and Newborns, and Effects on Infection

A prospective study of **80 IBD pregnant women** at tertiary hospitals (2012 - 2014).

Anti-TNFa monotherapy vs COMBO (39 anti TNFa + thiopurines); NO UNEXPOSED GROUP

Concentrations of anti-TNF agents were measured in blood samples from women at delivery, in umbilical cords, and in infants every 3 months until the drug was no longer detected.

	IFX concentration μg/ml			ADA concentration μg/ml		
	Last infusion < GW 30	Last infusion ≥ GW 30	*P* value	Last injection < GW 30	Last injection ≥ GW 30	*P* value
Total number	18 (41%)	26 (59%)		7 (19%)	29 (81%)	
Maternal blood	0.6 (0.0-3.3)	4.0 (0.0-22.2)	< .0001	0.3 (0.0-0.7)	2.1 (0.0-10.0)	.0006
Cord blood	2.2 (0.1-8.9)	10.0 (1.9-28.7)	< .0001	0.2 (0.0-1.2)	2.5 (0.0-12.1)	.0047

GW = gestational week

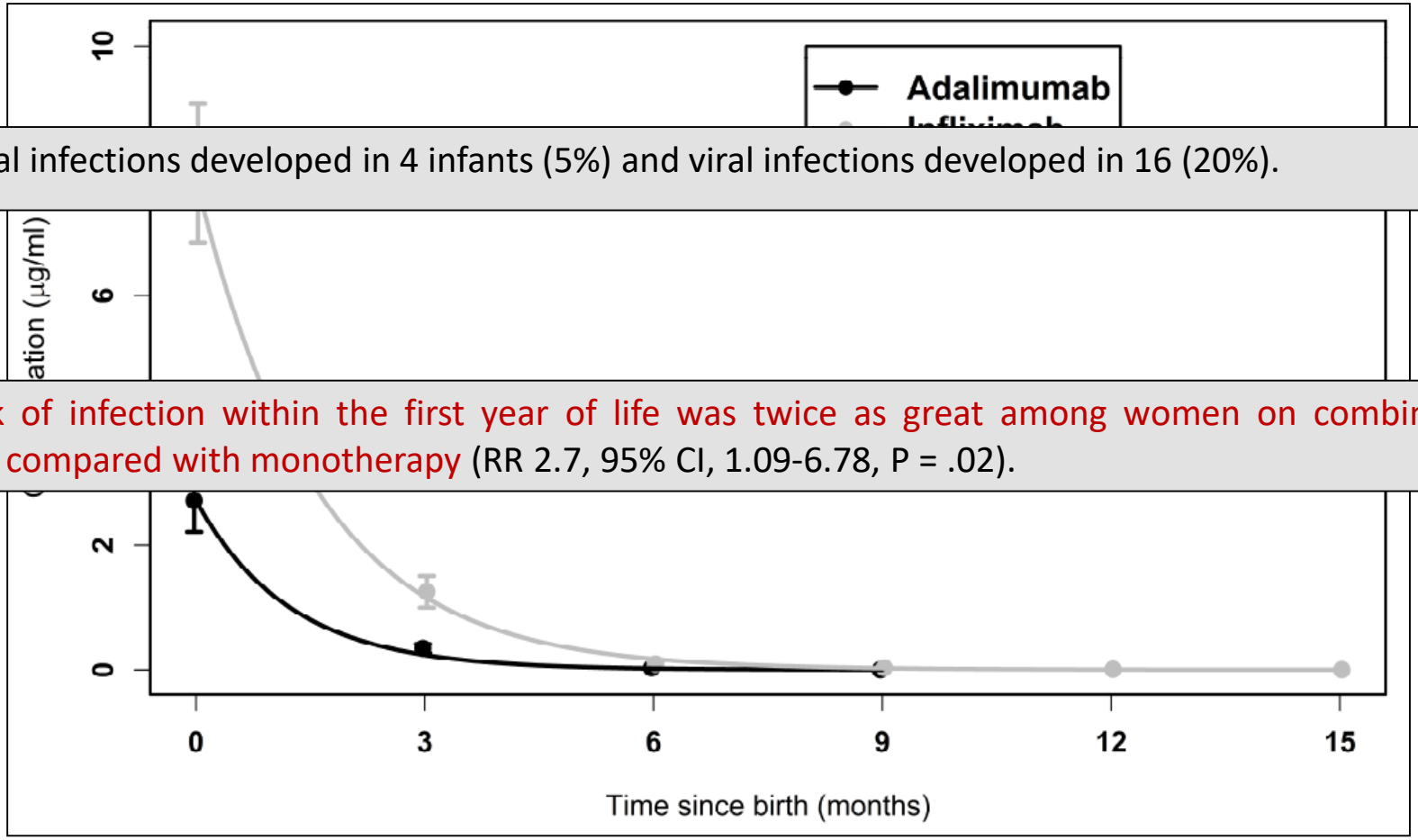
The time from last exposure to anti-TNF agent during pregnancy correlated inversely with concentration of the drugs in umbilical cord and in mothers

Julsgaard M, Gastroenterology 2016

Concentrations of Adalimumab and Infliximab in Mothers and Newborns, and Effects on Infection

Bacterial infections developed in 4 infants (5%) and viral infections developed in 16 (20%).

The risk of infection within the first year of life was twice as great among women on combination therapy compared with monotherapy (RR 2.7, 95% CI, 1.09-6.78, P = .02).



The mean time to drug clearance in infants was 4.0 months for ADA and 7.3 months for IFX.
Drugs were not detected in infants after 12 months of age

Julsgaard M, Gastroenterology 2016

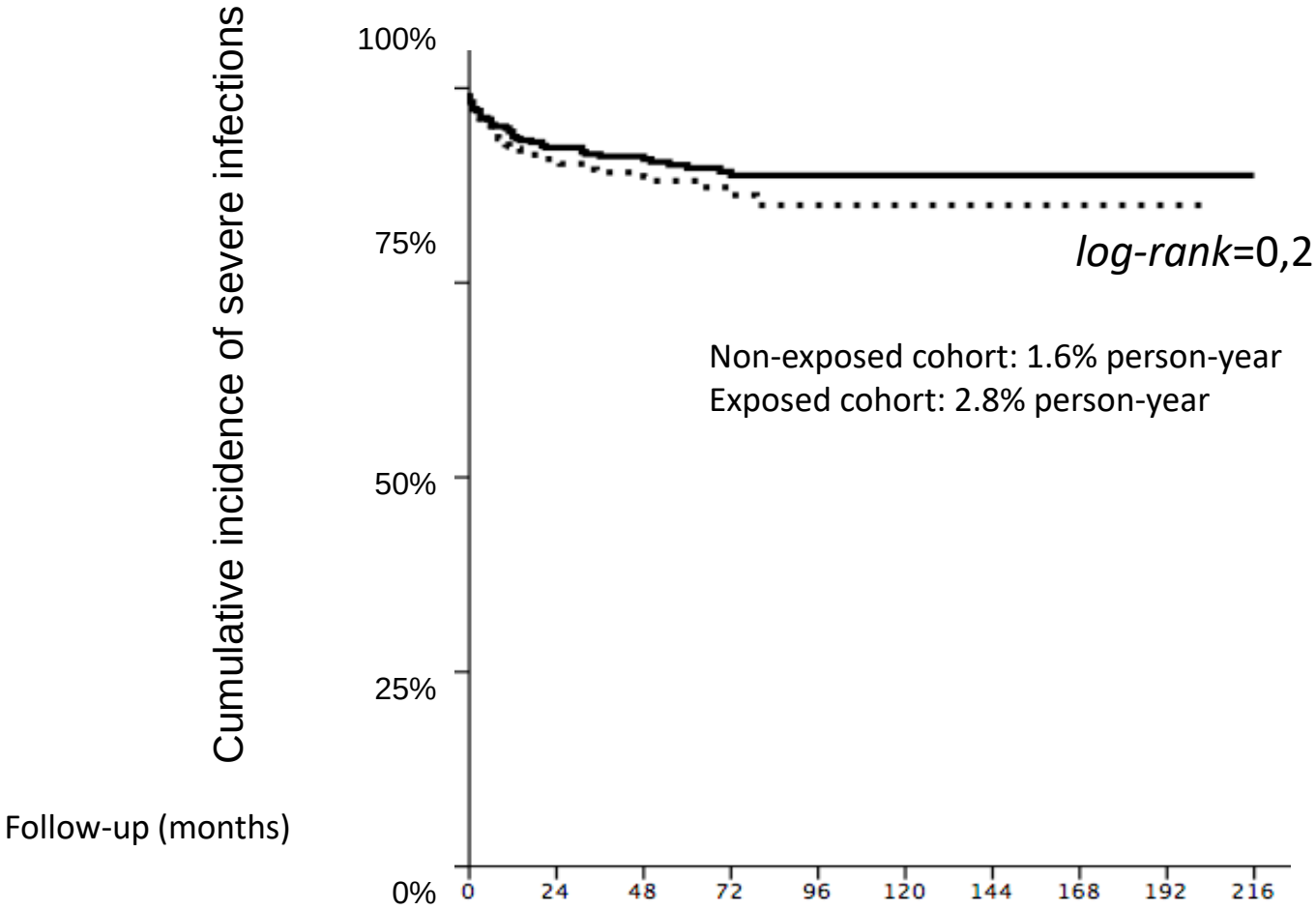
Long-Term Safety of *In Utero* Exposure to Anti-TNFα Drugs for the Treatment of Inflammatory Bowel Disease: Results from the Multicenter European TEDDY Study

M. Chaparro, MD, PhD[1], A. Verreth, MD[2], T. Lobaton, MD, PhD[3], E. Gravito-Soares, MD[4], M. Julsgaard, MD, PhD[5], E. Savarino, MD, PhD[6], F. Magro, MD, PhD[7], I. Avni Biron, MD[8], P. Lopez-Serrano, MD, PhD[9], M.J. Casanova, MD, PhD[1], M. Gompertz, MD[10], S. Vitor, MD[11], M. Arroyo, MD[12], D. Pugliese, MD[13], Y. Zabana, MD, PhD[14], R. Vicente, MD[15], M. Aguas, MD, PhD[16], A. Bar-Gil Shitrit, MD[17], A. Gutierrez, MD, PhD[18], G.A. Doherty, MB, PhD, FRCP[19], L. Fernandez-Salazar, MD[20], J. Martínez Cadilla, MD[21], J.M. Huguet, MD, PhD[22], A. O'Toole, MD[23], E. Stasi, MD[24], N. Manceñido Marcos, MD, PhD[25], A. Villoria, MD, PhD[26], K. Karmiris, MD, PhD, FEBGH[27], J.F. Rahier, MD, PhD[28], C. Rodriguez, MD[29], M. Diz-Lois Palomares, MD, PhD[30], G. Fiorino, MD, PhD[31], J.M. Benitez, MD[32], M. Principi, MD[33], T. Naftali, MD[34], C. Taxonera, MD, PhD[35], G. Mantzaris, MD, PhD[36], L. Sebkova, MD[37], B. Iade, MD[38], D. Lissner, MD[39], I. Ferrer Bradley, MD[40], A. Lopez-San Roman, MD, PhD[41], I. Marin-Jimenez, MD, PhD[42], O. Merino, MD[43], M. Sierra, MD[44], M. Van Domselaar, MD[45], F. Caprioli, MD, PhD[46], I. Guerra, MD[47], P. Peixe, MD[48], M. Piqueras, MD[49], I. Rodriguez-Lago, MD[50], Y. Ber, MD[51], K. van Hoeve, MD[52], P. Torres, MD[3], M. Gravito-Soares, MD[4], D. Rudbeck-Resdal, MD[5], O. Bartolo, MD[6], A. Peixoto, MD[7], G. Martin, MD[8], A. Armuzzi, MD, PhD[13], A. Garre, MSc[1], M.G. Donday, MSc[1], F.J. Martín de Carpi, MD[53] and J.P. Gisbert, MD, PhD, Professor[1]

Am J Gastroenterol 2018

Exposure to anti-TNF agents and serious infections

841 children (46 % exposed vs 62% not exposed during the third trimester)
median FU 47 months
The study did not provide any information about the occurrence of mild infections



Chaparro M, Am J Gastroenterol 2018

INFLAMMATORY BOWEL DISEASE

Long-Term Safety of *In Utero* Exposure to Anti-TNFα Drugs for the Treatment of Inflammatory Bowel Disease: Results from the Multicenter European TEDDY Study

M. Chaparro, MD, PhD[1], A. Verreth, MD[2], T. Lobaton, MD, PhD[3], E. Gravito-Soares, MD[4], M. Julsgaard, MD, PhD[5], E. Savarino, MD, PhD[6], F. Magro, MD, PhD[7], I. Avni Biron, MD[8], P. Lopez-Serrano, MD, PhD[9], M.J. Casanova, MD, PhD[1], M. Gompertz, MD[10], S. Vitor, MD[11], M. Arroyo, MD[12], D. Pugliese, MD[13], Y. Zabana, MD, PhD[14], R. Vicente, MD[15], M. Aguas, MD, PhD[16], A. Bar-Gil Shitrit, MD[17], A. Gutierrez, MD, PhD[18], G.A. Doherty, MB, PhD, FRCP[19], L. Fernandez-Salazar, MD[20], J. Martínez Cadilla, MD[21], J.M. Huguet, MD, PhD[22], A. O'Toole, MD[23], E. Stasi, MD[24], N. Manceñido Marcos, MD, PhD[25], A. Villoria, MD, PhD[26], K. Karmiris, MD, PhD, FEBGH[27], J.F. Rahier, MD, PhD[28], C. Rodriguez, MD[29], M. Diz-Lois Palomares, MD, PhD[30], G. Fiorino, MD, PhD[31], J.M. Benitez, MD[32], M. Principi, MD[33], T. Naftali, MD[34], C. Taxonera, MD, PhD[35], G. Mantzaris, MD, PhD[36], L. Sebkova, MD[37], B. Iade, MD[38], D. Lissner, MD[39], I. Ferrer Bradley, MD[40], A. Lopez-San Roman, MD, PhD[41], I. Marin-Jimenez, MD, PhD[42], O. Merino, MD[43], M. Sierra, MD[44], M. Van Domselaar, MD[45], F. Caprioli, MD, PhD[46], I. Guerra, MD[47], P. Peixe, MD[48], M. Piqueras, MD[49], I. Rodriguez-Lago, MD[50], Y. Ber, MD[51], K. van Hoeve, MD[52], P. Torres, MD[3], M. Gravito-Soares, MD[4], D. Rudbeck-Resdal, MD[5], O. Bartolo, MD[6], A. Peixoto, MD[7], G. Martin, MD[8], A. Armuzzi, MD, PhD[13], A. Garre, MSc[1], M.G. Donday, MSc[1], F.J. Martín de Carpi, MD[53] and J.P. Gisbert, MD, PhD, Professor[1]

In children exposed to anti-TNFα in utero no increase in neoplasms has been observed, although the length of follow-up was limited to a median follow up time of 4 years

Am J Gastroenterol 2018

HOW TO MINIMISE RISKS OF INFECTIONS?

- Avoiding combo-therapy
- Stopping anti-TNF alpha in the second trimester
- Avoiding live vaccines until the age of 6 months

Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety

Table 4 Child outcomes in the first year of life

Variable	Anti-TNF stop group (n=31)	Anti-TNF continue group (n=24)	p Value
Growth			
Normal (%)	30 (96.7)	24 (100.0)	1.00
Abnormal (%)	1 (3.3)	0 (0.0)	
Median no of infections (IQR)			
Requiring antibiotics	0 (0–1)	0 (0–1)	0.58
Requiring hospitalisation	0 (0–0)	0 (0–0)	0.74
Absolute number of infections requiring antibiotics (%)			
0	19 (61.3)	17 (73.9)	0.57
1–2	10 (30.3)	3 (13.3)	0.12
3–4	2 (6.5)	3 (13.3)	0.64
5–6	0 (0.0)	0 (0.0)	1.00
Allergies (%)	1 (3.0)	1 (4.2)	1.00
Eczema (%)	3 (9.1)	4 (16.7)	0.67
Adverse reactions to vaccines (%)	0 (0.0)	0 (0.0)	1.00

"**To limit anti-TNF exposure in utero**, anti-TNF can be stopped safely in the second trimester in women with IBD in sustained remission. In patients not in sustained remission, anti-TNF may be continued without clear additional risks to the fetus. We observed excellent 1-year child outcomes compared with children from non-IBD controls"

De Lima A, Gut 2015

Avoiding live vaccines until the age of 6 months

SHORT REPORT

Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's Disease

Kuldeep Cheent [a], Jonathan Nolan [a], Sohail Shariq [a], Liina Kiho [b], Arabinda Pal [a], Jayantha Arnold [a,*]

- ***High concentrations of anti TNFa in the neonate, sometimes exceeding the maternal concentration by a factor 2***
- ***Long halflife of anti TNFa, twice as long as in adults***
- ***AntiTNFa can still be detected in the child 12 mths after birth***

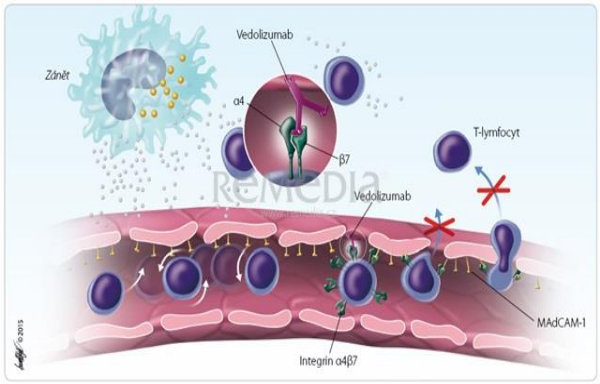
LIVE ATTENUATED VACCINATION (BCG, measles, mumps, rubella) SHOULD BE WITHHELD UNTIL 6 MONTHS AFTER BIRTH

SAFETY OF IMMUNOSUPPRESSIVE THERAPY IN PREGNANCY

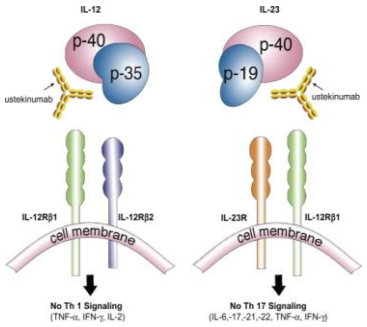
- Steroids
- Thiopurines
- Cyclosporine

- Anti TNF-a agents
  - Infliximab
  - Adalimumab
  - Golimumab

- Vedolizumab



- Ustekinumab



AP&T Alimentary Pharmacology and Therapeutics

Vedolizumab exposure in pregnancy: outcomes from clinical studies in inflammatory bowel disease

U. Mahadevan*, S. Vermeire†, K. Lasch‡, B. Abhyankar§, F. Bhayat§, A. Blake§ & M. Dubinsky¶

Table 1 | Number and outcome of pregnancies in female participants and partners of male participants in the clinical development programme

	Placebo (n^* = 3/4)			Vedolizumab (n^* = 24/15)			
Pregnancy outcome	Healthy volunteers	Patients with UC	Patients with CD	Healthy volunteers	Patients with UC	Patients with CD	Total (n^* = 27/19)
Live birth	0/0	1/2	0/1	0/0	4/5	6/3	11†/11
Congenital anomaly	0/0	0/0	0/0	1/0	0/0	0/0	1/0
Spontaneous abortion	1/0	0/0	1/0	0/0	2/1	2/1	6/2
Elective termination	0/0	0/0	0/1	0/0	2/1	3/1	5/3
Undocumented‡	0/0	0/0	0/0	0/0	1/1	3/2	4/3

CD, Crohn's disease; UC, ulcerative colitis.

*Number of pregnancies in female study participants/number of pregnancies in partners of male study participants.

†Includes the congenital anomaly outcome.

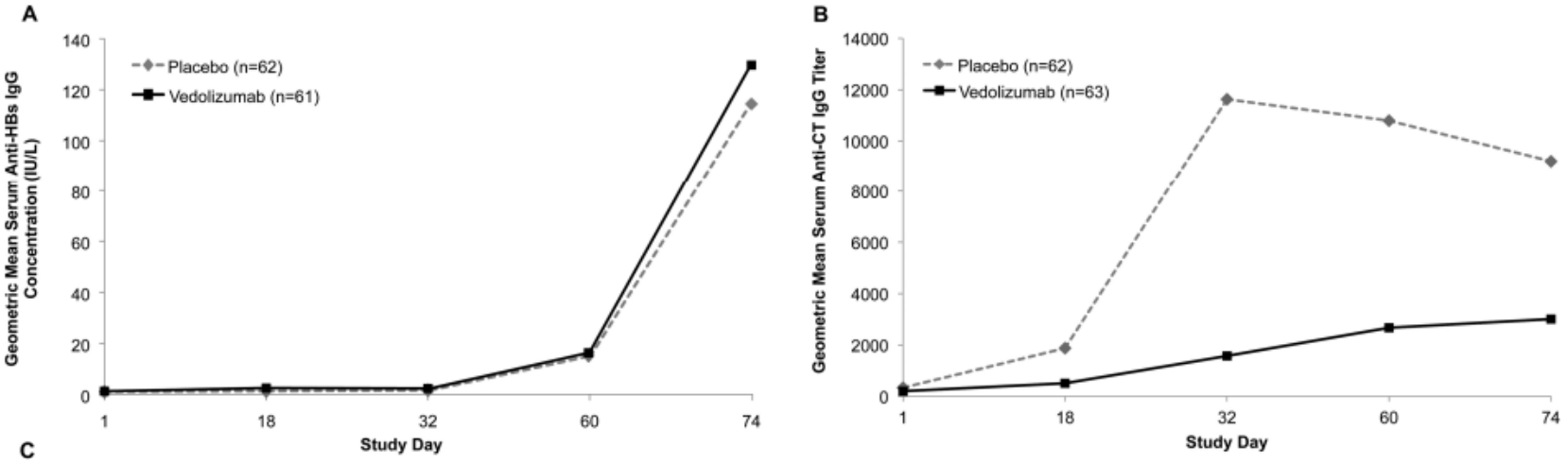
‡Includes pregnancies that were on-going at last participant contact.

Aliment Phamacol Ther 2017

ORIGINAL ARTICLE

Vedolizumab affects antibody responses to immunisation selectively in the gastrointestinal tract: randomised controlled trial results

Tim Wyant,[1] Tim Leach,[1] Serap Sankoh,[1] Yuemei Wang,[1] Jonathan Paolino,[2] Marcela F Pasetti,[3] Brian G Feagan,[4] Asit Parikh[5]



Vedolizumab did not alter the response to parenteral administered antigens (**hepatitis B**), but did reduce the response to oral antigens (**oral cholera vaccine**), supporting the hypothesis that its mechanism of action is selective for the gastrointestinal system.

Inflamm Bowel Dis 2014

Taylor & Francis
Taylor & Francis Group

Expert Review of Gastroenterology & Hepatology

ISSN: 1747-4124 (Print) 1747-4132 (Online) Journal homepage: http://www.tandfonline.com/loi/ierh20

Pregnant women with inflammatory bowel disease: the effects of biologicals on pregnancy, outcome of infants and the developing immune system

Jantien W. Wieringa, Gertjan J. Driessen & C. Janneke van der Woude

- There are no data available concerning. immunological development in children exposed to vedolizumab during pregnancy.

- There are no data concerning the risk of infection or malignancies in children who were exposed during pregnancy.

- For **anti-integrins and anti IL-12/23**, the numbers of exposed pregnancies are too small to draw any conclusions

Wieringa JW, Expert Rev Gastroenterol Hepatol 2018

ECCO Guidelines/Consensus Paper

The Second European Evidenced-Based Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease

C.J. van der Woude,[a*†] S. Ardizzone,[b] M.B. Bengtson,[c] G. Fiorino,[d] G. Fraser,[e] K. Katsanos,[f] S. Kolacek,[g] P. Juillerat,[h] A.G.M.G.J. Mulders,[i] N. Pedersen,[j] C. Selinger,[k] S. Sebastian,[l] A. Sturm,[m] Z. Zelinkova,[n] F. Magro,[o,p,q†] for the European Crohn's and Colitis Organization (ECCO)

ECCO Statement 4E

Since detectable levels of anti-TNF in the offspring are present in the first 6 months at least, live vaccines should be avoided in this period [EL5]

Current vaccination strategies with non-live vaccines do not differ from those for infants unexposed in utero to anti-TNF agents [EL4]

JCC 2015

HOW TO MINIMISE RISKS?

- Avoiding combo therapy
- Stopping anti-TNF alpha in the second trimester
- Avoiding live vaccines until the age of 6 months
- Enhancing preventive Health Care

Preventive HealthCare Among Postpartum Women With Inflammatory Bowel Disease: Results From the PIANO Registry

(628 women; at least 1 year of FU postpartum)

OVERALL HEALTHCARE MAINTENANCE COMPLIANCE

Preventive Measure	Compliance (%)
Cervical Cancer Screening	84%
Osteoporosis Screening	54%
Pneumococcal Vaccine	50%
Hepatitis A Vaccine	61%
Hepatitis B Vaccine	81%
Influenza Vaccine	72%

The unexposed group demonstrated lower pneumococcal vaccination rates than IMM-group, biologics-group and COMBO-group.

Biologics-group demonstrated lower cervical cancer screening rates than the unexposed.

The goal of preventive health care in IBD is to avoid preventable infections and advanced malignancies!

Mao EJ, Inflamm Bow Dis 2018

MINIMISING RISKS IN PREGNANCY

- Counseling prior conception:
  - Start pregnancy during remission
  - Active treatment, if necessary

- Avoid combo-therapy
- Stop biologics in the second trimester
- Avoid live vaccines until the age of 6 months in exposed infants
- Enhance preventive Health Care (screening/ vaccinations)


Thank you!