Zwangerschap en IBD:
Een ongelukkige combinatie?

C. Janneke van der Woude

Voordracht ter gelegenheid van de
Corrie Hermann Prijs 2017

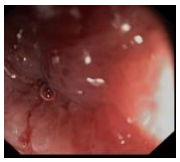
Tijdlijn zwangerschap met actieve ziekte

Zwangerschap (38 jaar)

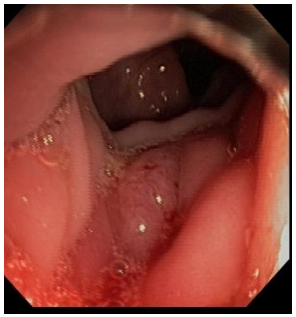
1995 1999 2000 2007 2007

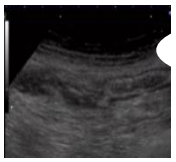
Week 12 16 22 33

Geen medicatie
week 24 OK voor
abcessen en fistels
Geboorte dood
kind



Ontsteking
prednison





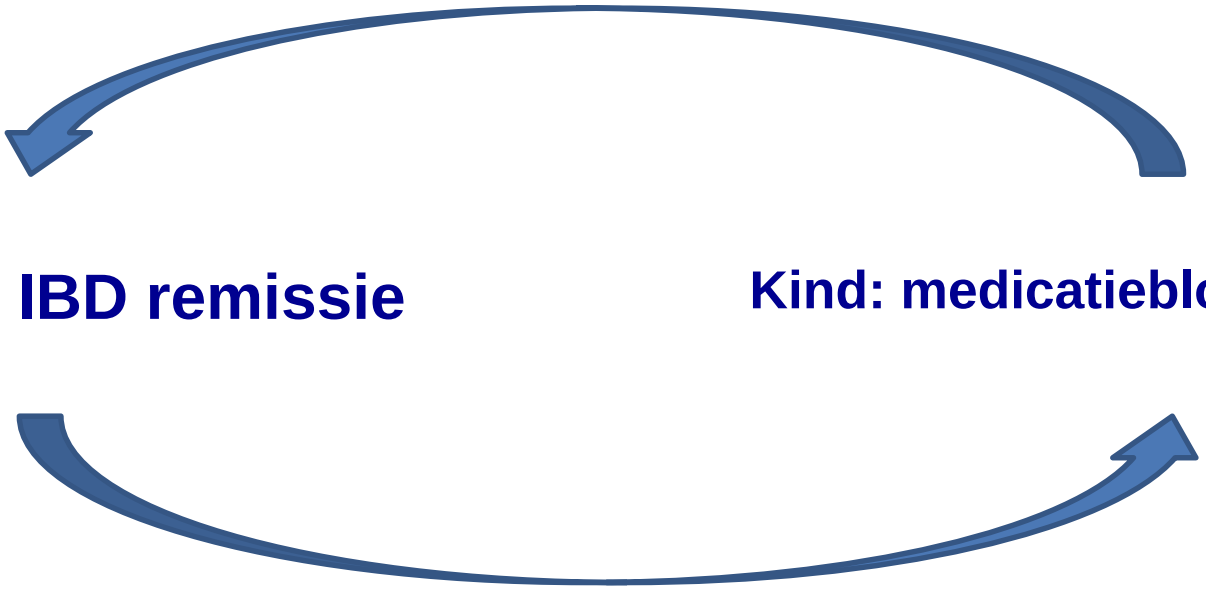
Campylobacter

Progressie
inflammatie

Intrauteriene
vriuchtdood

relaps

zwanger


Moeder: IBD remissie
Kind: medicatieblootstelling

Erasmus MC regels bij zwangerschapswens

1. Counsel

2. Ziekte remissie: voor *conceptie*

3. Laag risico medicatie continueren

4. Tijdens de zwangerschap geen uitstel behandeling opvlamming

5. Beperk *medicatie blootstelling in utero indien mogelijk*

Counsel voor de zwangerschap

Counseling

ECCO Statement 8 A

Appropriate referral for pre-pregnancy and pre-conception counseling should be available for all patients with IBD to advise and optimise management before conception [EL5]

Van der Woude et al. JCC 2015

Counseling zwangerschap bij IBD

- Ziekte remissie voor conceptie
- Doorgaan met medicatie
- Start foliumzuur, stop roken, lifestyle
- Bevalling
- Borstvoeding

Erasmus MC preconceptie cohort

N= 254	No preconception care (n=105)	Preconception care (n=149)	P-value
Maternal age in years (median)	31,0	30,8	0,843
Education level (median)	Middle secondary	Middle secondary	0,19
Marital status (n) Unmarried Married	 48 54	 73 74	0,701
Parity (n) Nulliparous Multiparous	 57 44	 111 36	0,001
BMI (median)	24,3	24,6	1,000
Referred by another hospital/GP (n)	34	40	0,482
Fertility treatment (n) IUI IVF ICSI Ovulation induction	9 2 5 0 2	24 5 14 1 4	0,001
Smoking 3 months prior to pregnancy (n)	16	28	0,308
Crohn's Disease (n)	75	108	0,888
Ulcerative colitis/ IBDU(n)	30	41	0,888
No IBD medication (n)	20	16	0.067
5-ASA (n)	23	34	1.000
Thiopurines (n)	40	58	1.000
Anti-TNF (n)	35	63	0.190
Presence of 1 or more extra intestinal manifestations (n)	21	30	1,000
Previous bowel surgery (n)	22	35	0,646
Disease duration in years (median)	7,8	6,4	0,033

Lima et al . Clin Gastroenterol Hepatol 2016

Uitkomsten moeder

	Control group (n=105)	Study Group (n=103)	P-Value	Crude OR	95% CI	Adjusted OR	95% CI
Folate intake (n)	46	87	0.0001	5.58	2.39-12.99	4.46	1.83-10.89
Smoking cessation (n)	1	19	0.0001	8.22	1.85-36.63	12.02	1.52-95.30
Patient discontinuation of IBD medication (n)	8	0	0.0033	-	-	-	-
Periconceptional disease activity (n)	16	12	0.68	0.79	0.35-1.78	0.77	0.31-1.92
Disease activity during pregnancy (n)	34	20	0.02	0.44	0.23-0.84	0.46	0.21-0.97

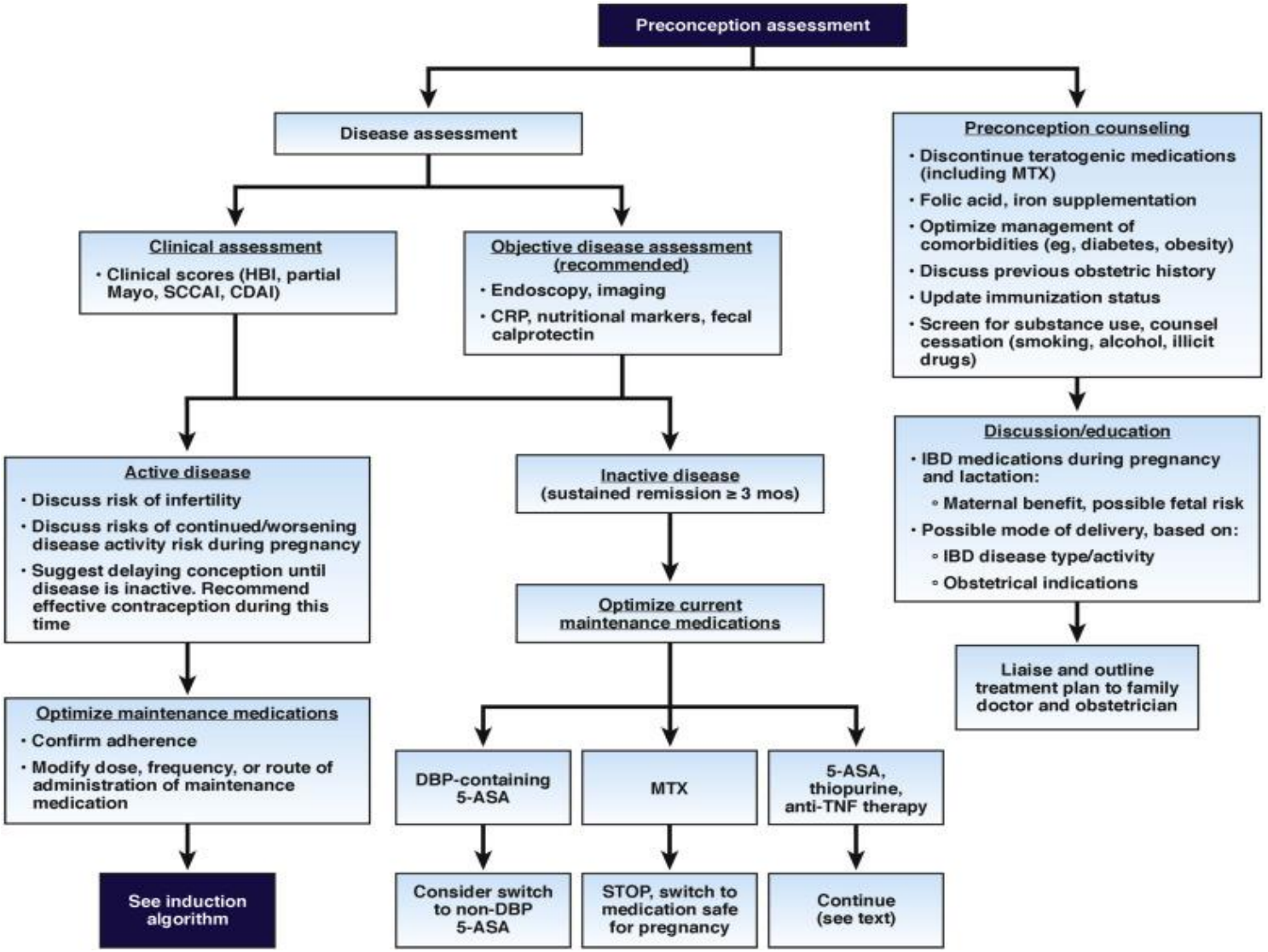
Lima et al . Clin Gastroenterol Hepatol 2016

Uitkomsten kind

	*PCC (n=129)***	*No PCC (n=162)*	*P****	*Crude OR (95% CI)*	*Adjusted OR (95% CI)*	*P****
Live births (%)	**97 (75.2)**	**127 (78.4)**	**0.58**	**0.84 (0.48-1.44)**	**0.79 (0.45-1.38)[a]**	**0.40**
Spontaneous abortions (%)	**26 (20.2)**	**31 (19.1)**	**0.88**	**1.07 (0.60-1.91)**	**1.10 (0.61-2.00)[a]**	**0.75**
Birth weight (g)	**3373 (2955-3679)**	**3363 (2829-3630)**	**0.52**	**-**	**-**	
Low birth weight (<2500 g) (%)	**7 (7.2)**	**16 (12.6)**	**0.19**	**0.53 (0.21-1.35)**	**0.08 (0.01-0.48)[b]**	**0.006**
Gestational age at birth (wks)	**38.4 (34.0-40.0)**	**38.0 (36.1-39.5)**	**0.50**	**-**	**-**	
Preterm birth (< 37 wks) (%)	**13 (13.4)**	**10 (7.9)**	**0.19**	**1.80 (0.75-4.31)**	**1.74 (0.73-4.16)[c]**	**0.22**
Small for gestational age (SGA)* (%)	**3 (3.1)**	**12 (9.4)**	**0.06**	**0.30 (0.08-1.09)**	**0.22 (0.05-1.00)[d]**	**0.05**
Congenital abnormalities (%)	**3 (3.1)**	**6 (4.7)**	**0.74**	**0.63 (0.16-2.60)**	**0.92 (0.20-4.14)[e]**	**0.91**

Lima et al . Clin Gastroenterol Hepatol 2016

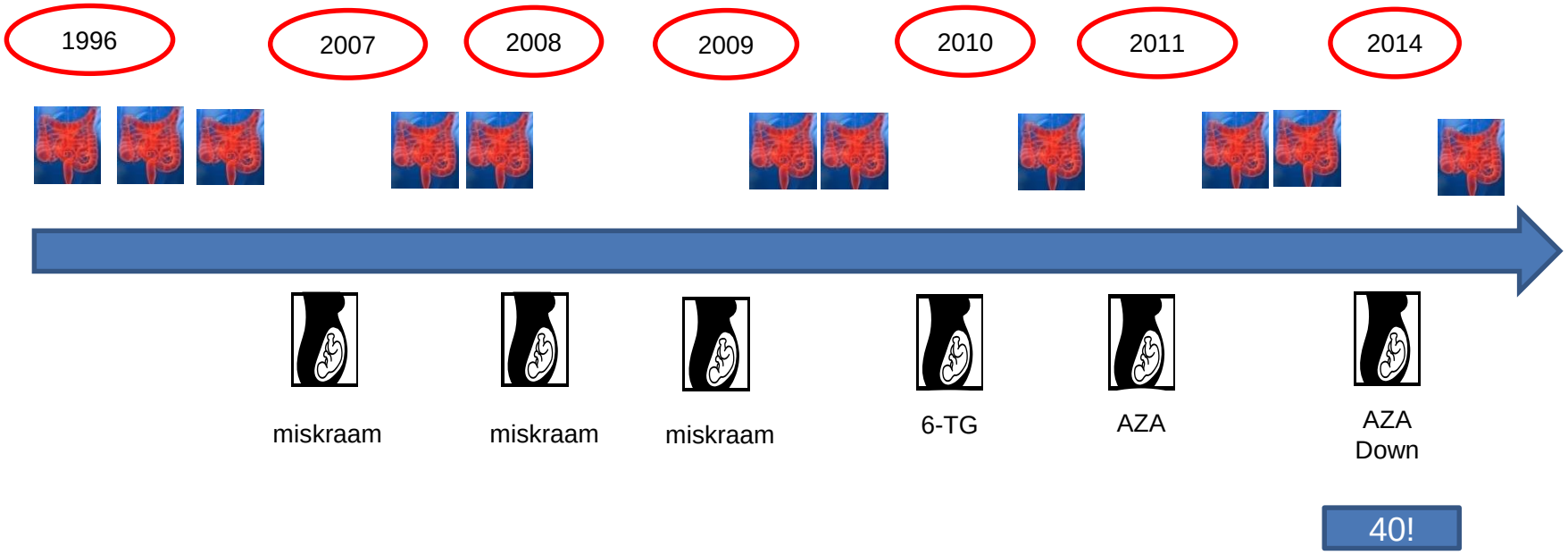
Flowchart counseling



Nguyen, Seow, Maxwell, Van der Woude et al. Gastroenterology 2016

Ziekte remissie: voor conceptie

Actieve ziekte en zwangerschap: geen goede combi



relaps

zwanger

IBD activiteit en zwangerschap

ECCO Statement 3A

If conception occurs at a time of quiescent disease, the risk of relapse is the same as in non pregnant women [EL3]

Conception occurring at a time of active disease increases the risk of persistent activity during pregnancy [EL3]

Van der Woude et al. JCC 2015

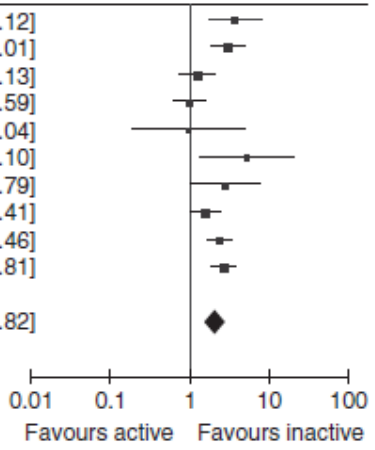
Ziekte activiteit en uitkomsten zwangerschap

Ulcerative colitis

Study or Subgroup	Active at Conception Events	Total	Inactive at Conception Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abramson (1951)	16	17	5	20	8.4%	3.76 [1.75, 8.12]
Banks (1957)	20	23	13	46	12.3%	3.08 [1.89, 5.01]
Bortoli (2011)	13	39	39	148	11.8%	1.26 [0.75, 2.13]
Crohn (1956)	16	38	31	74	12.7%	1.01 [0.63, 1.59]
DeDombal (1965)	1	3	27	80	2.9%	0.99 [0.19, 5.04]
MacDougall (1956)	30	60	2	21	4.0%	5.25 [1.37, 20.10]
McEwen (1972)	10	22	4	25	6.0%	2.84 [1.04, 7.79]
Mogadam (1981)	19	43	38	135	13.2%	1.57 [1.02, 2.41]
Nielson (1983)	14	19	41	133	14.2%	2.39 [1.65, 3.46]
Willoughby (1980)	38	55	33	129	14.6%	2.70 [1.92, 3.81]
Total (95% CI)		319		811	100.0%	2.08 [1.54, 2.82]
Total events	177		233			

Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 25.32$, df = 9 ($P = 0.003$); $I^2 = 64\%$

Test for overall effect: $Z = 4.74$ ($P < 0.00001$)

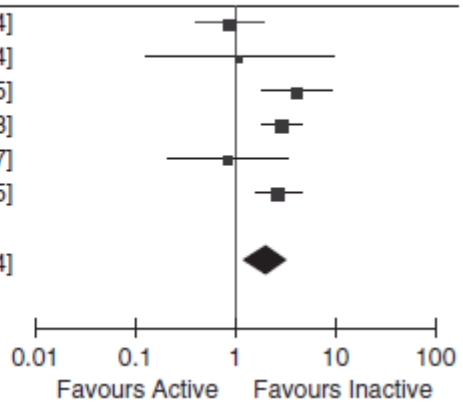


Crohn`s disease

Study or Subgroup	Active Events	Total	Inactive Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bortoli (2011)	5	19	38	126	18.1%	0.87 [0.39, 1.94]
Homan (1976)	1	10	3	33	4.9%	1.10 [0.13, 9.44]
Khosla (1984)	11	20	7	52	18.1%	4.09 [1.84, 9.05]
Mogadam (1981)	13	20	28	126	25.5%	2.92 [1.85, 4.63]
Morales (2000)	2	9	7	26	9.7%	0.83 [0.21, 3.27]
Woolfson (1990)	11	16	16	62	23.7%	2.66 [1.56, 4.55]
Total (95% CI)		94		425	100.0%	2.06 [1.23, 3.44]
Total events	43		99			

Heterogeneity: $\tau^2 = 0.22$; $\chi^2 = 12.30$, df = 5 ($P = 0.03$); $I^2 = 59\%$

Test for overall effect: $Z = 2.76$ ($P = 0.006$)



Abhyankar et al. Aliment Pharmacol Ther 2013

Risico op opvlamming

	Periconceptional disease activity			Disease activity during pregnancy		
	Crude OR (95% CI)	Adjusted OR (95% CI)	P	Crude OR (95% CI)	Adjusted OR (95% CI)	P
Disease duration (yrs)	0.97 (0.90-1.04)	0.96 (0.89-1.03) [a]	0.26	0.95 (0.90-1.01)	0.97 (0.91-1.03) [a]	0.35
Ulcerative colitis	0.61 (0.29-1.28)	0.63 (0.28-1.41) [b]	0.26	2.66 (1.53-4.63)	3.71 (1.86-7.40) [e]	**0.0001**
Disease activity in year preceding conception	6.76 (3.32-13.76)	9.24 (4.06-20.93) [c]	**0.0001**	2.13 (1.26-3.62)	0.81 (0.40-1.64) [f]	0.55
Smoking	0.90 (0.38-2.17)	0.98 (0.39-2.44) [d]	0.96	1.12 (0.46-2.73)	1.01 (0.37-2.74) [d]	0.98
Periconceptional disease activity	-	-	-	7.80 (3.87-15.72)	7.29 (3.41-15.57) [g]	**0.0001**

[a] Adjusted for education level, smoking, previous surgery for IBD, and the use of IS or biologicals

[b] Adjusted for age, smoking, previous IBD surgery and the use of IS or biologicals

[c] Adjusted for disease duration, smoking, previous IBD surgery and the use of IS or biologicals

[d] Adjusted for age and education level

[e] Adjusted for age, smoking, previous IBD surgery, the use of IS or biologicals and periconceptional disease activity

[f] Adjusted for disease duration, smoking, previous IBD surgery, the use of IS or biologicals and periconceptional disease activity

[g] Adjusted for age, smoking and disease activity in the year preceding conception

de Lima A, et al, Am J Ge 2016

Laag risico medicatie continueren

Medicatie en zwangerschap

ECCO Statement 5A

Appropriate treatment of IBD should be maintained in those patients who wish to conceive, in order to reduce the risk of flares during pregnancy [EL5]

ECCO Statement 5B

Most drugs used for the treatment of IBD are considered to be of low risk during pregnancy [EL3] However, methotrexate and thalidomide, are contraindicated [EL3]

Vrouw geboren in 1992

2003 Ernstige ziekte van Crohn

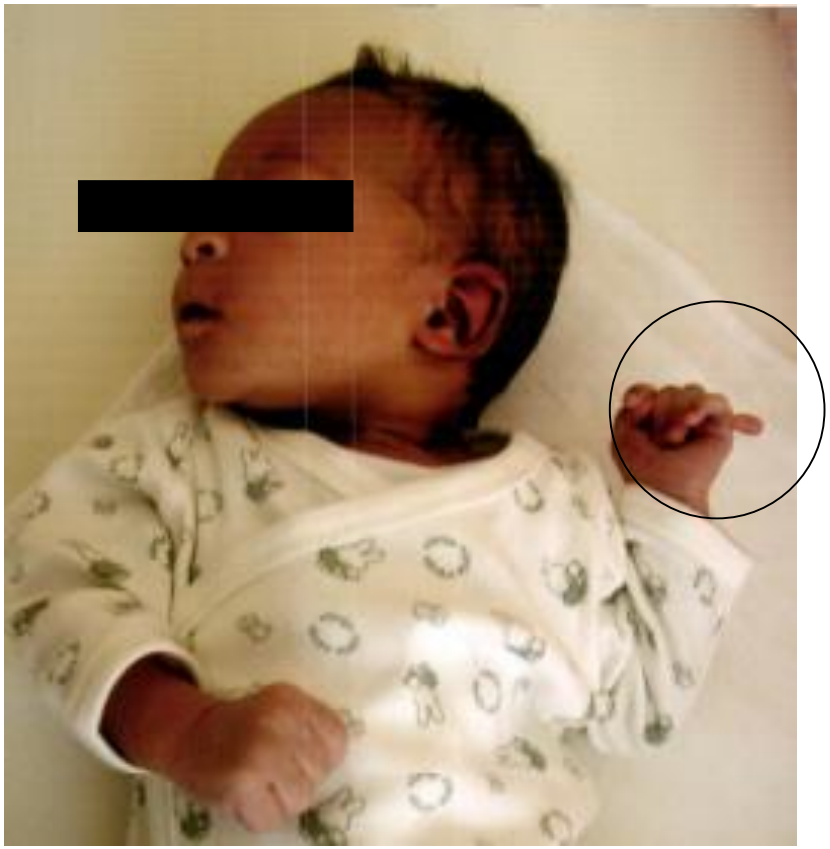
2004 Pyoderma gangrenosum

2007 Uveitis: MTX en anti-TNF

2009 Juni: geen kinderwens

18 en 26 weken zwanger……

- Echo (3D):geen afwijkingen
- MTX gestopt



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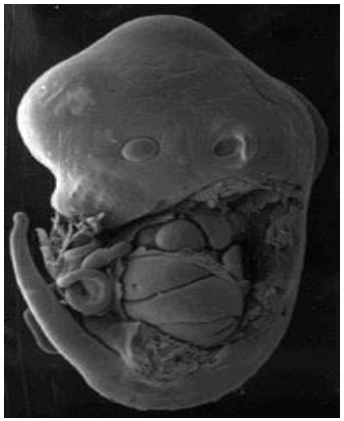
Tijdlijn ontwikkeling embryo



Spermio + Oogenesis	Blastogenesis	Organo-genesis	Fetogenesis

sterility	rejection	severe malformation	mal-formation	functional anomalities

IBD medicatie en zwangerschap

Drug	During pregnancy
Mesalazine	Low risk
Sulfasalazine	Low risk
Corticosteroids	Low risk
Thiopurines	Low risk, limited data on 6-TG
Anti-TNF agents	Low risk
Vedolizumab	*Unknown*
Ustekinumab	*Unknown*
Methotrexate	Contraindicated
Thalidomide	Contraindicated

Van der Woude et al. JCC 2015

Geen uitstel behandeling opvlamming

Medicatie bij opvlamming tijdens zwangerschap

ECCO Statement 5A

Acute flares during pregnancy carry a high risk of adverse maternal and fetal outcome, and are best treated appropriately and without delay to prevent these complications [EL3]

Van der Woude et al. JCC 2015

Prednison tijdens de zwangerschap

- **Prednison en prednisolon inactivatie door 11ß-HSD**

- **Dexamethasone, bethametasone, hydrocortisone passeren de placenta**

Van Runnard Heimel Obstet Gynecol Surv 2005; Beitins et al Pediatr 1972; Moore&Martin J Perinatol 2001

Prednison en zwangerschap

Geen verhoogd risico schisis

Table 3: Association between corticosteroid use during first trimester of pregnancy and isolated orofacial clefts among 832 636 live births

		Cleft lip with or without cleft palate		Cleft palate alone	
Corticosteroid use	No. of live births	No. (prevalence*)	Adjusted OR† (95% CI)	No. (prevalence*)	Adjusted OR‡ (95% CI)
Any use	51 973	57 (1.10)	1.05 (0.80–1.38)	27 (0.52)	1.23 (0.83–1.82)
No use	780 663	818 (1.05)	1.00	330 (0.42)	1.00
Route of administration					
Oral					
Yes	2 195	0 (0.00)	NA	0 (0.00)	NA
No	830 441	875 (1.05)	1.00	357 (0.43)	1.00

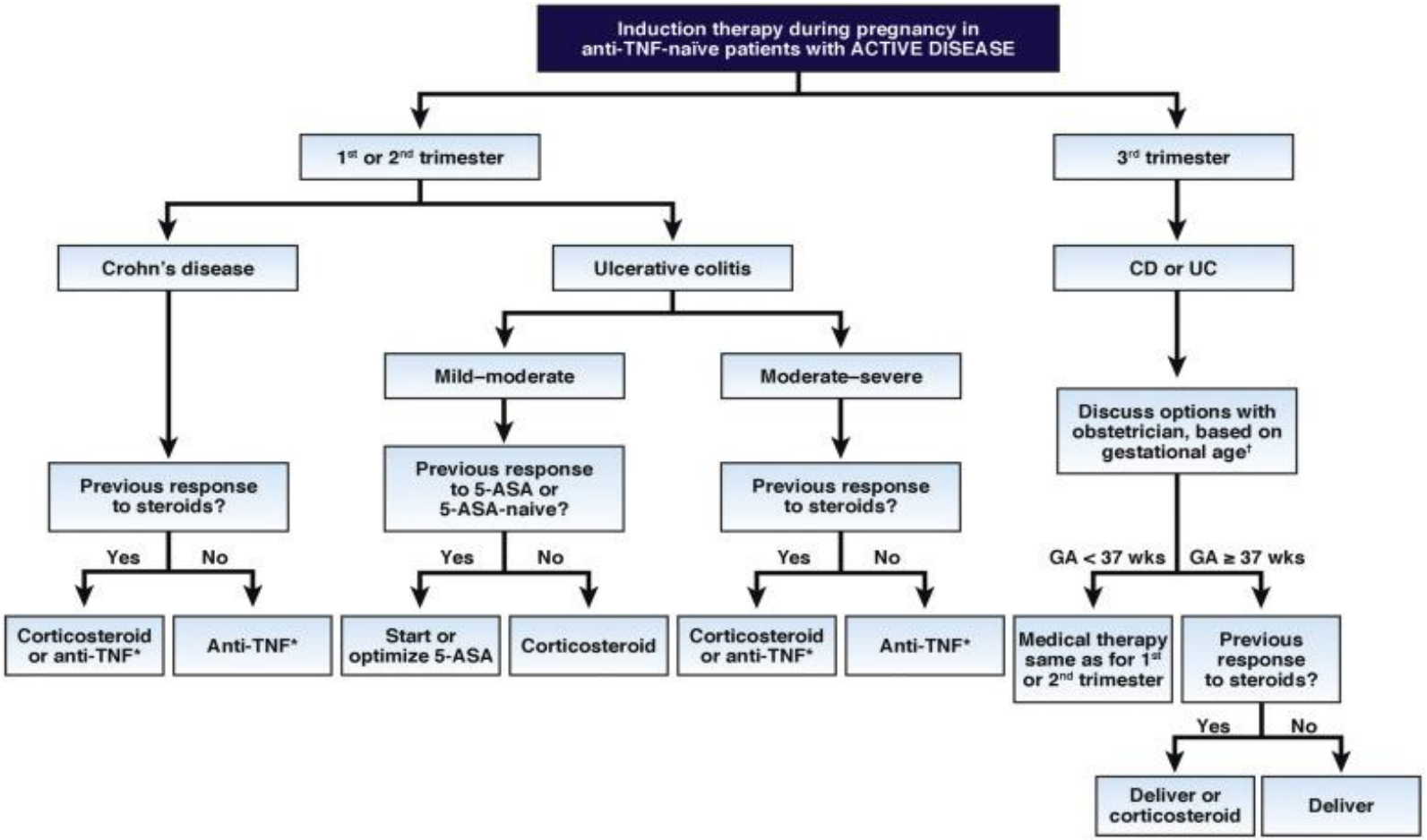
Hviid A, et al. CMAJ 2011

Prednison en zwangerschap

- **Langdurig gebruik prednison <15 mg/dag geen negatieve kinduitkomsten**
- **Boven 15mg prednison/dag verhoogd risico op prematuriteit en intrauteriene infectie**
- **Risico op bijnierschorsinsufficientie kind**
- **Hypertensie en diabetes**

Ostensen&Forger, Nat Rev Rheumatol 2009
Cowchock et al. Am J Obstet Gynecol 1992

Flowchart opvlamming tijdens de zwangerschap



Nguyen, Seow, Maxwell, van der Woude et al . Gastroenterology 2016

Beperk medicatie blootstelling in utero

“Treat to target”

Variable	Cases (had endoscopy) n= 42	Matched controls (no endoscopy) n= 42	P value
Live births (%)	40 (95.2)	32 (76.2)	.03
Low birth weight (%)	6 (15.0)	4 (12.5)	1.00
Preterm birth (%)	8 (20.0)	4 (12.5)	1.00
Congenital abnormalities (%)	0 (0.0)	3 (7.1)	.24

de Lima A, et al, JCC 2015

Zwangerschap en beeldvorming

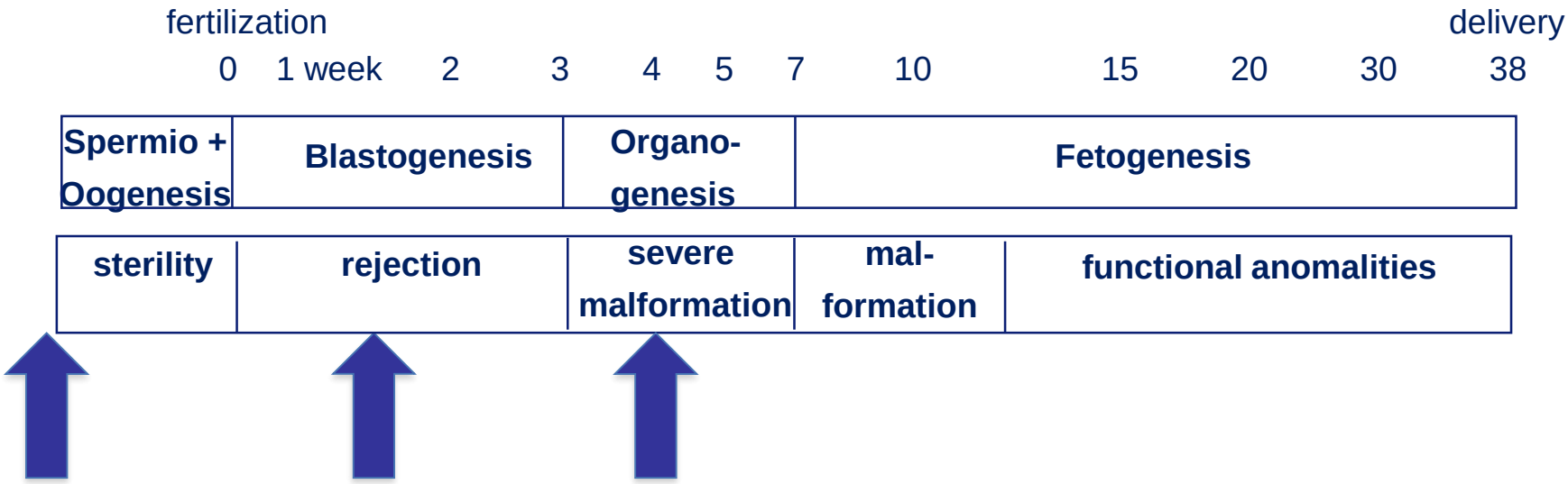
Table 6 Imaging and endoscopy during pregnancy

Procedure	Recommendations
Ultrasound	Preferred imaging technique during pregnancy
MRI	Low risk, without gadolinium
CT scan	Avoid, if necessary postpone until week 20
Upper endoscopy	Low risk, insufficient lower sphincter: increased risk of aspiration
Lower endoscopy	Low risk, avoid abdominal pressure
ERCP	Low risk, therapeutic indication, experienced endoscopists
	Limit radiation exposure, avoid hard copy x-ray films
Sedation	
Midazolam	Low risk, if possible avoid in first trimester
Propofol	Low risk
Fentanyl	Low risk
Bowel preparations	
PEG	Low risk

Endoscopy can be performed, the first trimester may be avoided, fetal monitoring is necessary, especially when sedation is needed, consult the obstetrician. Pregnant patients in the 2nd or 3rd trimester should be placed in the left pelvic tilt or left lateral position to avoid vena cava or aortic compression. Take care of adequate maternal oxygen and blood pressure for optimal placental perfusion.

Van der Woude CJ, et al. Gut 2014

Anti-TNF en reproductie

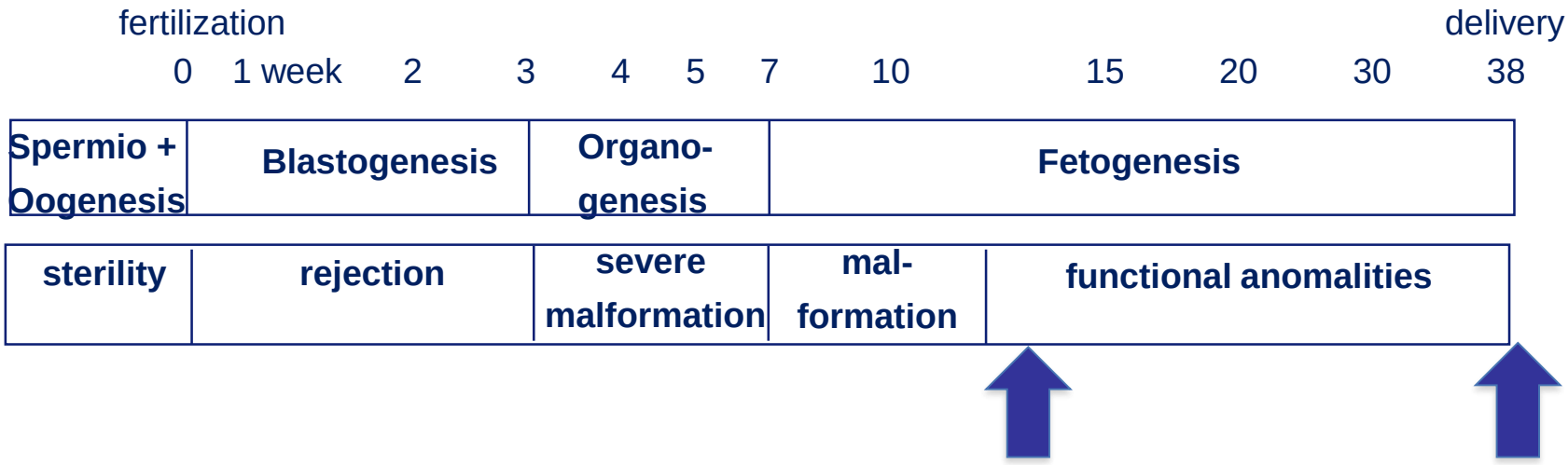


Fertiliteit normaal, niet meer miskramen

Waarschijnlijk geen verhoogd risico congenitale afwijkingen

Winger et al. Am J Reprod Immunol 2008 Prokesch et al. Histochem Cell Biol 2016 Bröms et al. Clin Gastroenterol Hepatol. 2016 Shihab et al. JCC 2016

Anti-TNF en reproductie



Stop op week 22-24: geen verhoogd risico op opvlamming wanneer remissie > 6m

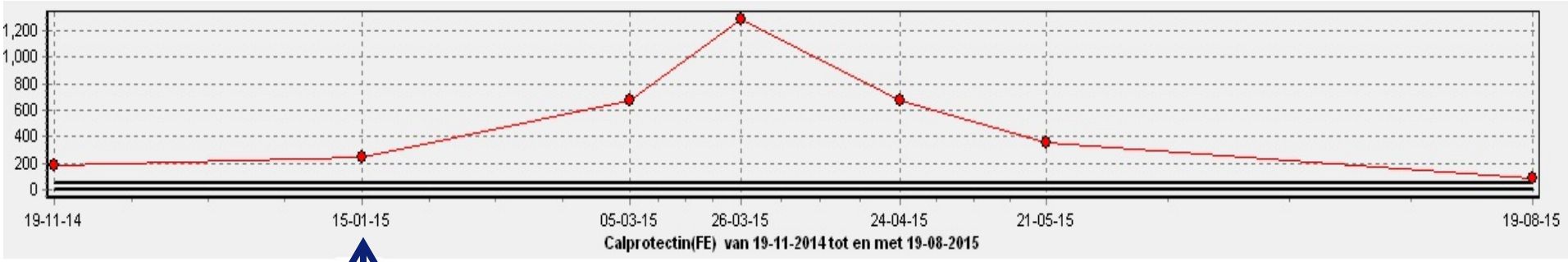
Continueren: hoge anti-TNF spiegels in het kind, persisteren tot 1 jaar na geboorte

Kind uitkomsten goed

Casus over neutropenie in pasgeborenen en na BCG vaccinatie overlijden

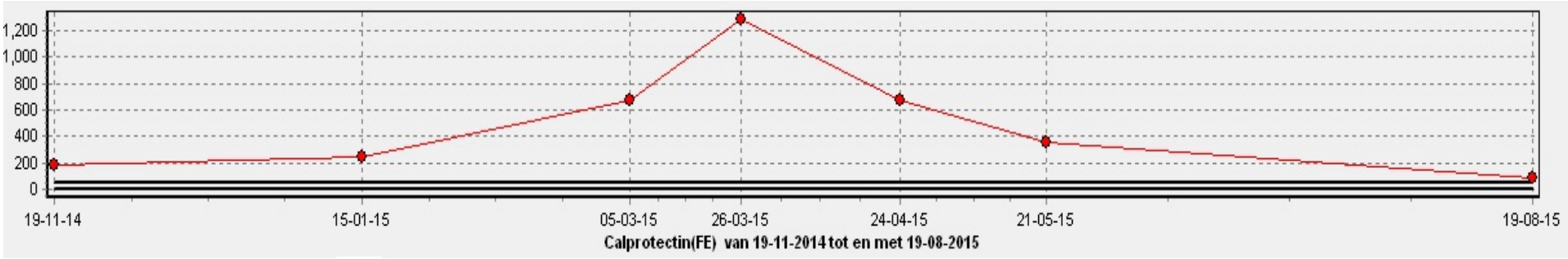
De Lima et al. Gut 2016 Julsgaard et al. Gastroenterology 2016 Cheent et al. JCC 2010 Guiddir et al. Pediatrics 2014

Staken adalimumab in remissie



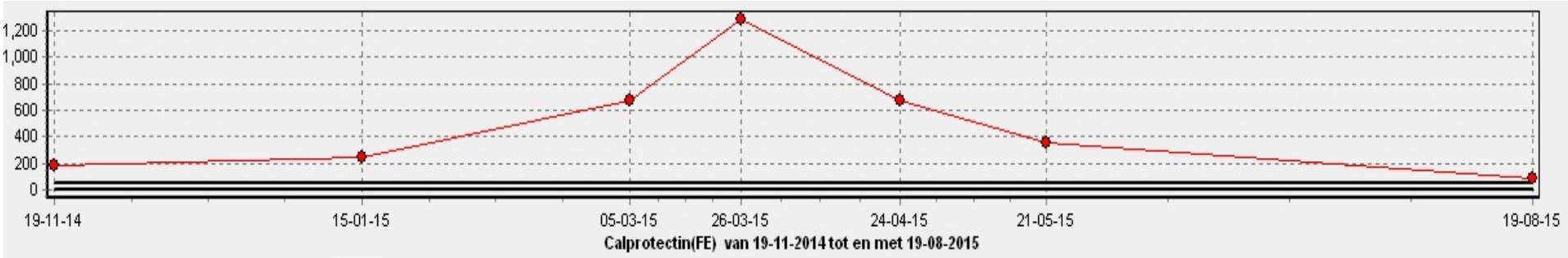
17 weken zwanger: remissie

Staken adalimumab in remissie



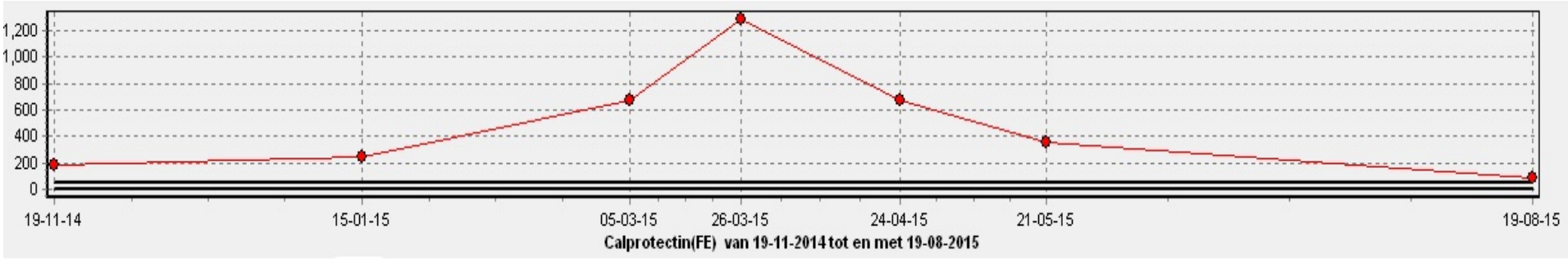
21 weken zwanger: laatste ADA

Staken adalimumab in remissie



26 weken zwanger:opvlamming

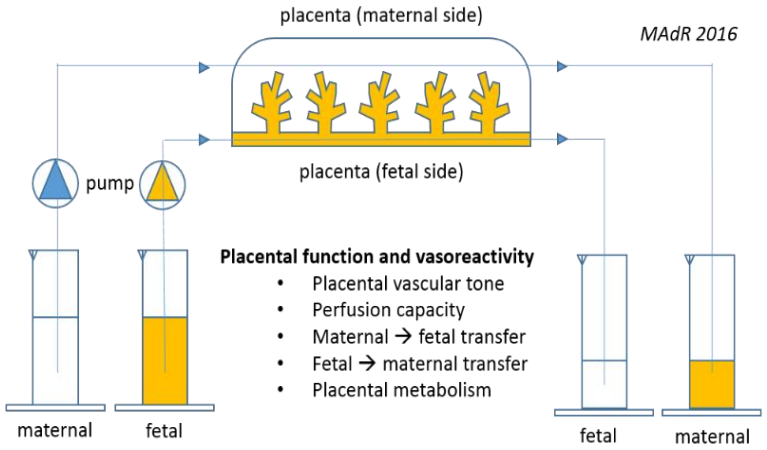
Staken adalimumab in remissie

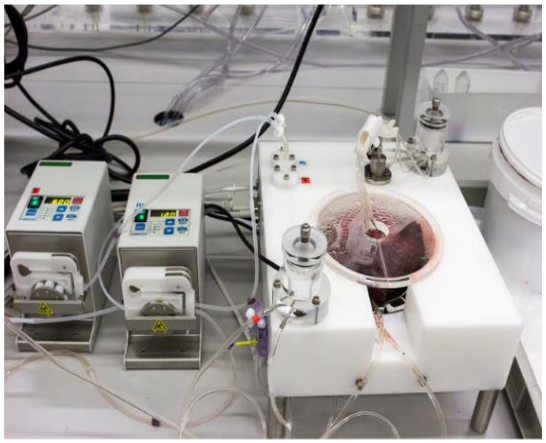


27 weken zwanger: herstart ADA

Toekomstige doelen

- Immuunsysteem van kinderen blootgesteld in utero: effect vaccinaties
- Langetermijn uitkomsten kinderen van moeders met IBD
- Voor medicatie registratie data over transfer placenta





In conclusie

- Elke vruchtbare vrouw is een kandidaat voor preconceptie zorg
- Bij elke IBD patiënt moet kinderwens een onderdeel zijn van de behandelstrategie
- De meeste medicijnen kunnen gecontinueerd worden tijdens de zwangerschap
- Indien mogelijk: Beperk blootstelling in utero


Genetische verwantschap is
niet een voorwaarde voor een
supergezin