Post ECTRIMS 2019
Nieuwe ontwikkelingen
in het algemeen

Jop Mostert

Rijnstate

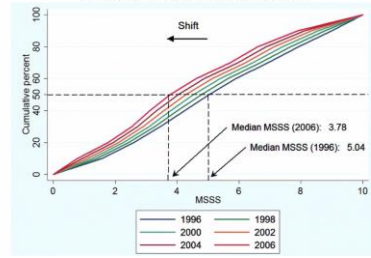
Inhoud

- Beloop MS
- Zwangerschap
- E-health: Steps
- Vitamine D

Is there a trend for decreasing MS disability with increasing calendar year during 'DMT era'?

- New York State MS Consortium (N=6,238; from 1996 - 2007)
- MSBase (N=11,108 from 20 countries; from 1996 - 2010)

Trend for lower MSSS with higher Calendar year of enrollment was present after controlling for age at enrollment, diagnostic delay, disease duration, sex and ethnicity



Net average gains in years at disability milestones over 13-year follow up:

- EDSS 3/3.5 subgroup was on **3.6 years** of age older at the end of the enrollment period compared to the beginning of period (95% CI, 1.2–6.0)
- EDSS 4/4.5 subgroup was **7.9 years older** (95% CI, 5.5–10.5)
- EDSS 6/6.5 group was **4.9 years older** (95% CI, 2.4–7.6).

Conclusions

- Over the course of first 'treatment decade', there was a significant trend for milder disability and older age at disability milestones on enrollment in two large MS datasets

  Trends were observed across disease durations/disability spectrum except for the most disabled/longest duration subgroups

- These results are broadly consistent with the hypothesis that use of DMTs earlier in the disease has a positive effect on the long-term course of the disease

'Disease progression is slower than previously reported'

	London Ontario, 1989[1]	Lyon, 2003[2]	Olmsted county, 2004[3]	British Columbia 2006[4]	Newcastle NSW 2007[5]	Nova Scotia, 2009[6]	Rennes, 2010[7]	Sweden, 2017[8]
Cohort size	1099	1844	201	2837	159	1607	2054	12703
EDSS 6 (Cannot walk without cane' (median))	15.0 years	20.1 years	28.6 years	27.9 years	27.0 years	32.4 years	18.0 years	30.4 years

Majority of follow-up time was free from disease-modifying drug exposure

1. Weinshenker Brain 1989
2. Confavreux Brain 2003
3. Pittock Neurology 2004
4. Tremlett Neurology 2006
5. McLeod J Neurol Sci 2007
6. Brown Mult Scler. 2009
7. Leray Brain 2010
8. Manouchehrinia MSJ 2017

Reflections

What we know

The MS natural disease course: published studies

Suggest that disability progressing is slower in more contemporary cohorts, even prior to the mainstream introduction of disease-modifying drugs

Contributing factors and uncertainties

The source populations & recognition of MS

Inequalities in health access and paternalism

MS clinic attendees differ from non-attendee:

Only patients known to have MS can be included in a study of MS

MS patients with rapidly progressing disease likely overrepresented in older studies

➔ *MS itself may not have changed, but recognition of MS likely has changed*

Future considerations

The MS prodrome… *Is a measurable, symptomatic phase*

➔*Suggests earlier window of opportunity to identify MS*

➔*May result in further 'apparent' slowing of MS progression - 'lead time bias'*

What is the known problem?

- 60% of pregnant women take prescribed medication during pregnancy, 50% during the first trimester, even more over the counter medication
- Animal studies are not always predictive if the risk occurs in humans
- For most drugs it is not known if they are safe or not safe
- And the process of information gain is very slow (91% unknown time 0-87,8% 10 year later)*
- PV data: lack of an accurate denominator, missing data often > 50%, direction of bias?
- Pregnancy registries lack of a control group, slow recruitment
- The mean time for a drug from undetermined risk to more precise risk takes 27 (95%CI,26-28) years **
- Fortunately teratogenic effects have been demonstrated for only 30 treatments in humans, some of them used in neurology (antiepileptic drug/VPA and others) or neuroimmunology off label (MMF/MTX)

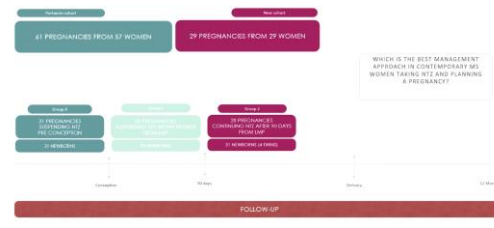
*Lo et al 2002, **Adam et al 2011

DMT	Animal Data	1. trimester exposure	Exposure throughout pregnancy	Recommendation
IFN-beta	abortive effect	No association with negative pregnancy outcomes (n>2500)	No association with negative pregnancy outcomes (n<100)	Continuation up to conception; consider maintaining if necessary New label awaited September 2019
GLAT	-	No association with negative pregnancy outcomes (n>2,500)	No association with negative pregnancy outcomes (n>216)	Continuation up to conception or beyond if necessary
DMF	low fetal weight, delayed ossification, abortive effects	No association with negative pregnancy outcomes (n>300)	Only single cases beyond first trimester	Discontinue with contraception or consider discontinuation with positive pregnancy testing
FTY	reproductive toxicity teratogenicity	Slightly increased teratogenic possible (n>700)	No association with negative pregnancy outcomes (n<17), potential risk can not be ruled out	- Pregnancy tests obligatory prior first dose - Effective contraception during treatment and up to 2 month - Discontinue 2 months before conception
TFM	teratogenicity	Slightly increased abortive possible So far no teratogenicity pregnancy outcomes (n>208)	Only single cases beyond first trimester	- Effective contraception during treatment - accelerated elimination procedure as long as plasma concentration is above 0.02 mg/l

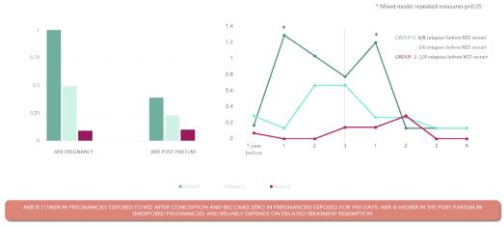
DMT	Animal Data	1. trimester exposure	Exposure throughout pregnancy	Recommendation
NTZ	abortive effect hematological abnormalities	Slightly increased abortive and teratogenic risk can not be ruled out, but unlikely (n>494)	Hematological abnormalities (n<53) Birth weight?	- May consider continuation up to conception and beyond after careful risk-benefit evaluation - Monitor neonatal blood count in case of in-utero exposure
ALZ	abortive effect lymphozytopenia	Slightly increased abortive risk can not be ruled out (n<167)	-	- Pregnancy tests obligatory prior each cycle - Discontinue 4 months before conception - Monitor neonatal lymphocyte count in case of in-utero exposure - Monitor closely secondary autoimmune diseases
OCR/ RTX	B-cell depletion	No association with negative pregnancy outcomes (n<150)	Preterm birth, Birth weight B cells newborn	- May consider conception immediately after last infusion after careful risk-benefit evaluation - Re-dosing in case of no pregnancy after 6 months - Consider redosing in case of severe relapses during pregnancy - monitor neonatal B-cell count in case of in-utero exposure - If reduced eventually postpone vaccinations
CLAD	Embryoletality teratogenicity	Potential teratogenic risk can not be ruled out (n<16) 10 ET, 3 healthy newborns	-	- Pregnancy tests obligatory prior each cycle - Effective contraception during treatment and up to 6 month - Discontinue 6 months before conception - Consider embryo-toxicological counseling in case of in-utero exposure

STUDY DESIGN

ITALIAN OBSERVATIONAL MULTICENTER RESEARCH TRIAL



ARR BEFORE AND DURING PREGNANCY AND POST-PARTUM



ARR IS LOWER IN PREGNANCIES EXPOSED TO NTZ AFTER CONCEPTION AND BECOMES ZERO IN PREGNANCIES EXPOSED FOR 180 DAYS. ARR IS HIGHER IN THE POST-PARTUM IN UNEXPOSED PREGNANCIES AND REMAINS LOWER ON DELAYED TREATMENT RESUMPTION

FETAL DEMOGRAPHIC AND CLINICAL DATA

Mean (SD)	Group 0 n=29		Group 2 n=35	p-value
Gestational age (weeks)	38.16 (3.58)	39.17 (2.39)	38.16 (2.89)	0.523
Birth weight (g)	2864.06 (552.22)	2951 (537.66)	2813 (456.69)	0.890
Birth length (cm)	48.57 (1.93)	48.83 (2.74)	47.31 (4.79)	0.331
Anemia	0	0	5 (3/5 premature)	-
Birth defects (newborns, type and classification of defect)	1 (0.03%) Undescended testicle (minor)	4 (13%) Congenital clubfoot (major) Renal asymetric (minor) Hypospadias unspecified (minor) Thyroglossal duct cyst (minor) Cleft palate (major) Gastroesophageal reflux (minor)	4 (12%) Patent foramen ovale (major) Gastrointestinal reflux (minor) Bifid clitoris atheletica (major) Pulmonary valve stenosis (major) Pulmonary insufficiency (minor) Malposition of the aorta (major)	-

* twin pregnancy

FETAL PARAMETERS ARE NOT DIFFERENT ACROSS GROUPS

ANEMIA IS MORE FREQUENT IN NEWBORNS EXPOSED FOR > 90 DAYS, NEVERTHELESS AN INTERACTION WITH PREMATURITY CANNOT BE EXCLUDED.

BIRTH DEFECTS FREQUENCY IS HIGHER IN PREGNANCIES EXPOSED TO NTZ. ALBEIT CONFOUNDING FACTORS (TWINNING) SHOULD BE TAKEN INTO ACCOUNT

Large Molecules & Other Safe Treatments

	large molecule drugs	description	detectable in breastmilk?	likelihood of transluminal transfer?*	expected effects with infant exposure	compatible with lactation?
Multiple Sclerosis						
	glatiramer acetate	(4.7-13kD) heterogeneous strings of amino acids	Not tested, unlikely	yes, as with any amino acid	none	yes
	IFN-betas	18-44kD glycoproteins	0.0006% relative infant dose	exceedingly low	flu-like symptoms	yes
	monoclonal antibodies					
	natalizumab	IgG4	<1:200 of maternal serum level;	exceedingly low	-	yes, if needed
	rituximab	IgG1	~1:240 of maternal serum level or lower**	exceedingly low	-	yes, if needed
	ocrelizumab	IgG1	Not tested	exceedingly low	-	yes, if needed
Migraine	***CGRP antagonists***	IgG2	Not tested	exceedingly low	-	Yes, if needed*
TE Stroke/CVST	**LMW Heparin**	2kD-8kD	Not detectable	exceedingly low	-	**yes**

*non-pharmacological treatments mainstay for migraine prevention. High dose riboflavin, magnesium, propranolol, TCAs are also safe for breastfeeding

**LaHue S etal. P4.2-097 AAN, Wednesday May 8, 2019*

Courtesy Dr. Longer Gould

Conclusion

1. Breastfeeding is not harmful – exclusive breastfeeding may be beneficial in women with milder disease (low pregnancy relapse frequency and severity)
2. Breastfeeding should NOT be discouraged in favor of resuming MS medications in most women
3. Choose treatments compatible with breastfeeding (injectables, mAbs) instead of foregoing nursing if needed and women want to breastfed
4. Cladribine: 1 week after last tablet ok*
5. More data on BF under medication and longer children follow up is needed
6. If a women does not want to breastfeed, start early (7-14 days) with MS treatment, especially in active disease

Remote Ambulatory Monitoring vs Traditional Assessments

Traditional Metrics:

- Clinic-based assessments → Snapshots of function (e.g. EDSS)
- Patient-reported measures → recall bias

Remote Ambulatory Monitoring:

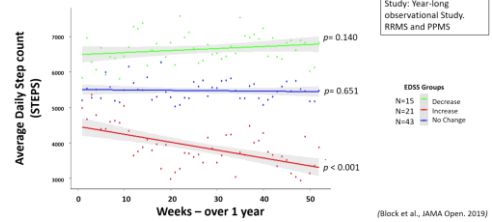
Average Daily Step Count (STEPS) → Objective

- Represents what people actually do in the ecological environment, rather than what they are capable of doing in a clinic setting
- STEPS can capture change, when traditional measures are unresponsive

(Block et al., Plos One. 2016; Block et al., Journal of Neurology. 2016; Block et al., JAMA Open. 2019; Motl et al., Acta Neurol Scand. 2013 & Motl et al., Plos One. 2017)

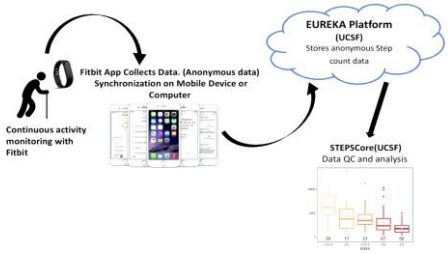
Background: Changes in Step Count Over 1 Year are Reflected in EDSS Change

Results from the FITriMS Study: Year-long observational Study. RRMS and PPMS



(Block et al., JAMA Open. 2019)

Methods: Daily Step Count Monitoring



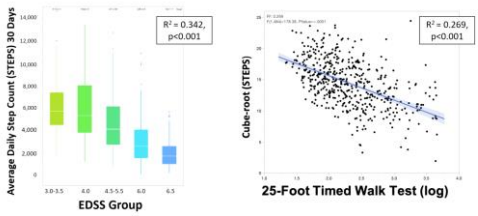
Results: Patient Characteristics

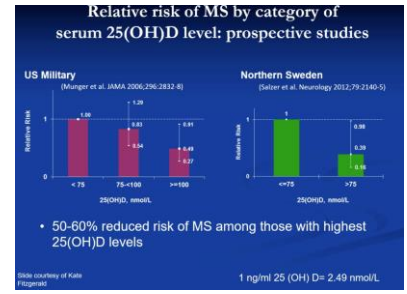
492 enrolled patients with full STEPS data at the time of analysis

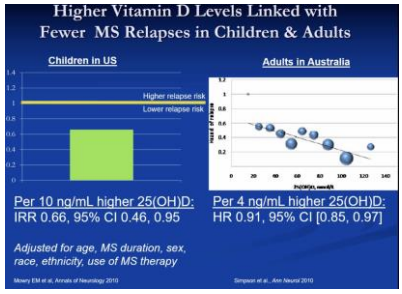
90 centres
(USA: 40, Europe: 39, Canada: 8, Australia: 3)

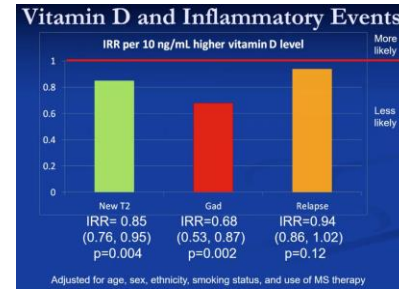
Demographic, Clinical & MRI	
SPMS: N (%)	311 (63.2)
Women: N (%)	262 (53.3)
Age: years (mean, SD)	52.7 (7.8)
EDSS: median (IQR)	6.0 (4.5 - 6.0)
Disease Duration: years (median, IQR)	10.6 (0.75 - 31.3)
T25FW (mean, SD)	11.49 (7.05)
T2 volume (mean, SD)	19.61 (17.42)
GD+ Lesions: N (%)	28 (5.7%)
STEPS (average step count, first 30 days): mean (SD)	3,699 (2,962)

Greater STEPS Correlates with Better Disability Scores and Faster Walking Speeds

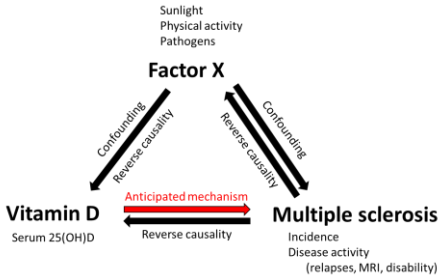








Vitamine D and MS



Verrichte RCT's

AUTHOR	YEAR (20..)	N	PHENO-TYPE	TREAT-MENT	DURATION (MONTHS)	PRIMARY ENDPOINT (T1)	SECONDS/ EXPLOR ENDPOINT
Stein	10	23	RR	-	6	Gd⁺T1& newT2=	Trend EDSS↑Rel↑
Kampman	12	68	RR	-	24	-	ARR=,MSFC= ,EDSS=
Soilu-Hänninen	12	66	RR	IFNβ	12	newT2=	Gd⁺T1↓
Golan	13	21	RR	IFNβ	24	-	ARR=,EDSS=
Sotirchos	16	40	RR	-	6	-	ARR=
O'Connel	17	32	CIS	-	6	-	ARR=,NEDA= ,EDSS=,MRI=
Camu	19	129	RR	IFNβ	24	ARR=	Gd⁺T1↓
Hupperts	19	229	RR	IFNβ	12	NEDA=	Gd⁺T1&new T2↓

Conclusions

- Vitamin D levels: inversely associated with MS risk and, in early established MS, inflammatory activity/brain atrophy
  - May not be uniform across racial/ethnic groups
  - Risk studies: possibly stronger role of UV light itself, especially in non-Caucasians
  - Prognostic studies: may not apply to later stages of MS
- Randomized MS trials published to date using higher doses of vitamin D (as add-on to interferon beta) have not met primary endpoints
- Also no major safety signals from [relatively short] MS trials
  - Safety of mega-doses not certain, & long-term effects unknown
- Decision should consider individual patient characteristics