INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

RHEUMATOLOGIE
& IMMUNOLOGIE

EULAR Highlights 2023

Reproduktion & Schwangerschaft bei Rheumaerkrankungen

Frauke Förger

29. Juni 2023

1) EULAR abstract about
Fertility in men with inflammatory arthritis

Why I chose this abstract?

- Knowledge gap

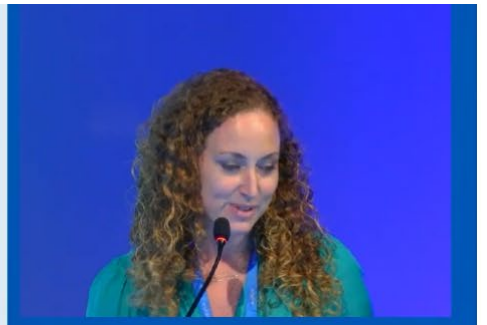
OP0262

Increased fertility among 10865 men with chronic inflammatory joint disease in Norway

Gudrun D Sigmo

Objective

- To examine whether inflammatory joint diseases (IJDs) have an impact on men's fertility, measured as number of children per man and proportion of childless men



Gudrun D. Sigmo

Increased fertility among 10865 men with chronic inflammatory joint diseases in Norway.

OP0262

Increased fertility among 10865 men with chronic inflammatory joint disease in Norway

Gudrun D Sigmo

Methods

- Nation-wide, population-based cohort study
- Studypopulation:
  - Patiens: Men with IJDs (*n* = 10,865) collected from the Norwegian Arthritis Register in 2021
  - Controls: Men without IJDs obtained from the National Population Register (*n* = 54,325), individually matched 1:5 on birth year, and county of residence
- Analyses
  - Mean number of children per man in the patient group vs the comparison group
    - Compared using paired *t*-tests
  - Proportion of childless men
    - Compared using Cochran–Mantel–Haenszel chi-squared tests

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Gudrun D Sigmo

Results

- Mean number of children per man
  - Patients: 1.80
  - Control group: 1.69
  - $p < 0.001$
- Percent childless men
  - Patients: 21%
  - Control group 27%
  - $p < 0.001$

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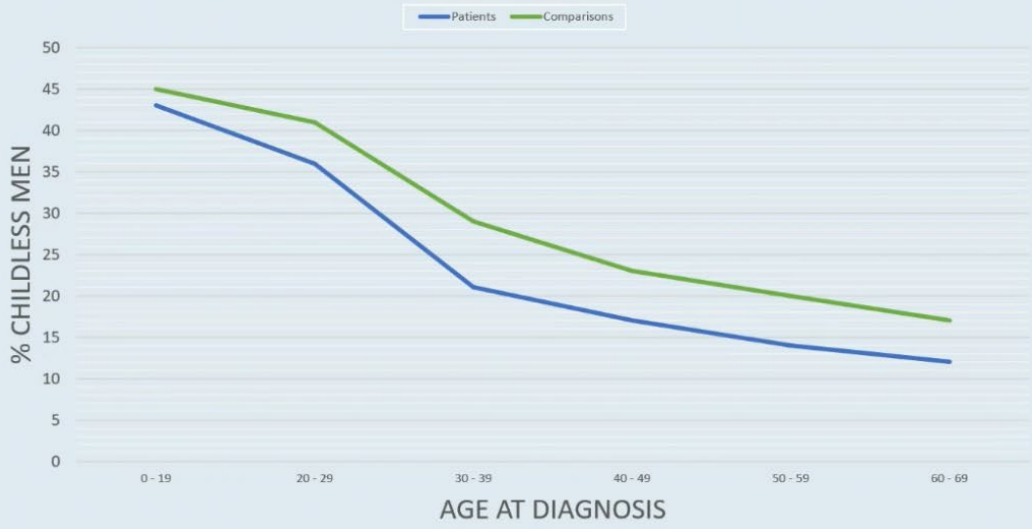
Proportion of childless men according to age at diagnosis



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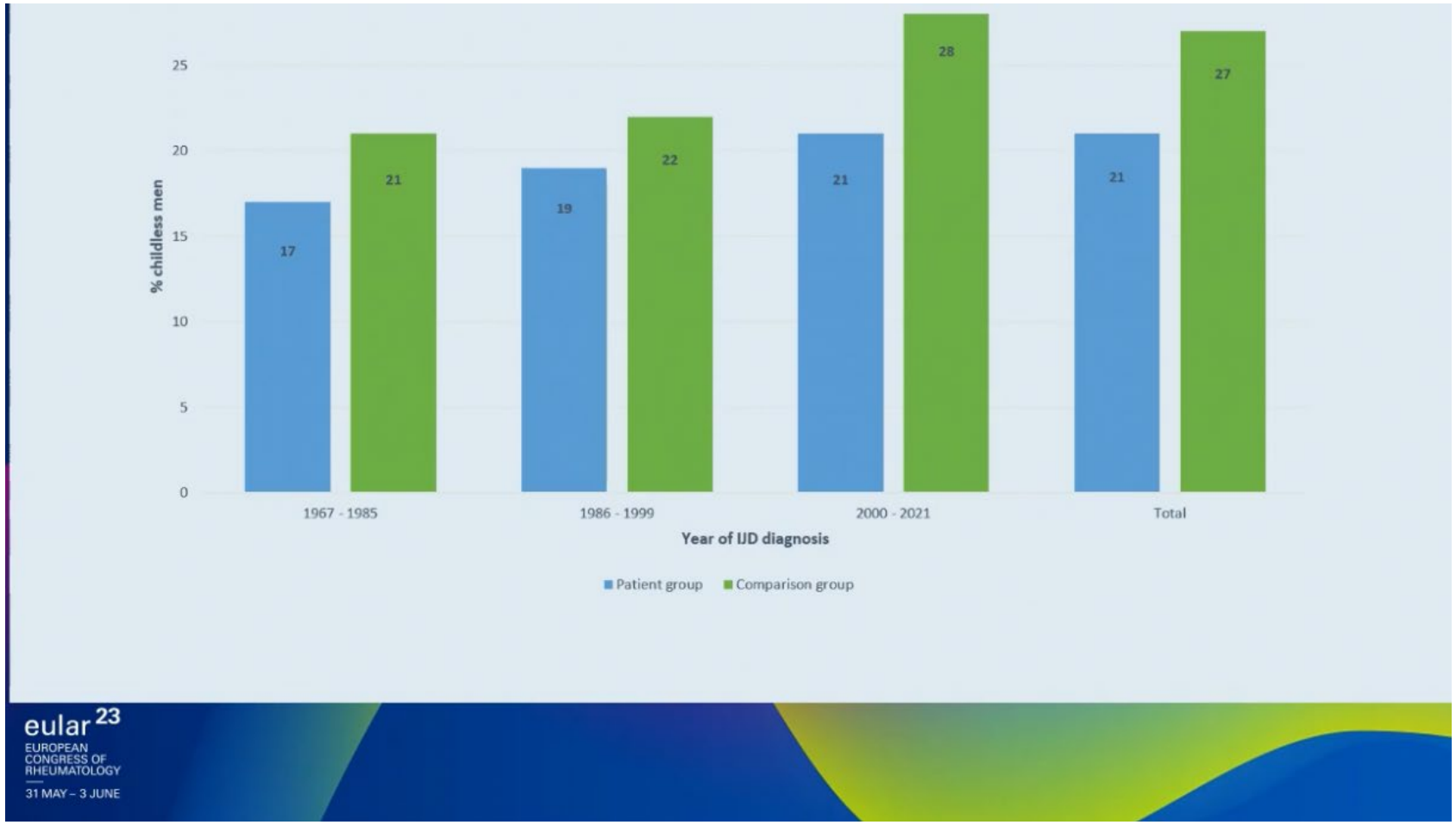

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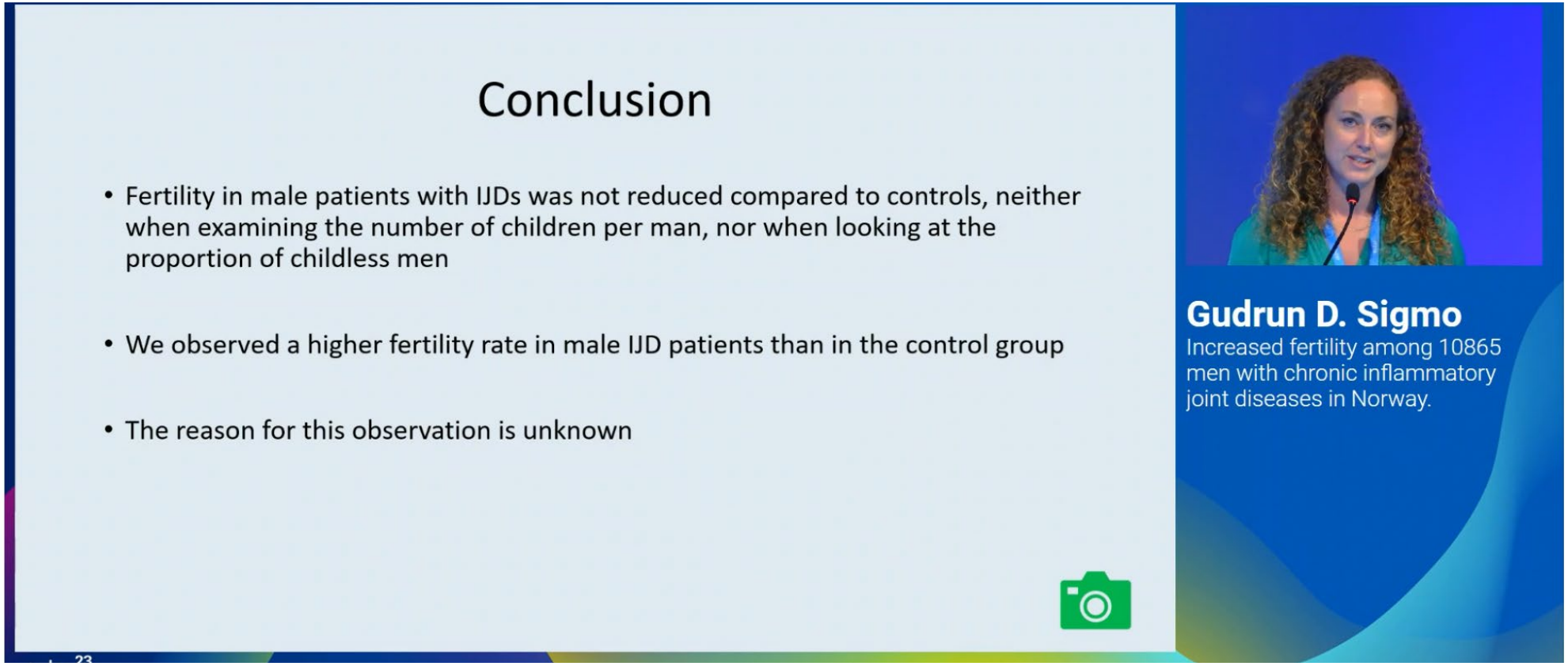

2) EULAR abstract about MTX polyglutamates analysed in semen

Why I chose this abstract?

- Never analysed before
- Adding to data on MTX & semen

Erasmus MC
Universitair Medisch Centrum Rotterdam

OP0224

iFAME

Lack of folylpolyglutamate synthetase activity and methotrexate polyglutamylation as underlying mechanisms explaining *why methotrexate does not impair sperm quality*

A proof of concept translational study (Part of the iFAME-MTX)

Perez-Garcia L.F.[1] (l.perez@erasmusmc.nl)

Röder E.[1], Krijthe B.P.[1,2], Kranenburg-van Koppen L.J.C.[1,3], van Adrichem R.[1], Zirkzee E.[4], Griffioen P.H.[5], Peeters K.[6], Lin M.[7], Struijs E.A.[7], Jansen G.[8], van Doorn M.B.A.[9], de Jonge R.[7], Dohle G.R.[10], Dolhain R.J.E.M.[1]

1.Department of Rheumatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. 2.Department of Rheumatology, Sint Franciscus Vlietland Group, Rotterdam, The Netherlands. 3.Department of Rheumatology, IJsselland Hospital, Rotterdam, The Netherlands. 4.Department of Rheumatology, Maasstad Ziekenhuis, Rotterdam, The Netherlands.5.Department of Clinical Chemistry, Erasmus MC, University Medical Center Rotterdam , Rotterdam, The Netherlands. 6.Centre for Reproductive Medicine, Antwerp University Hospital, Edegem, and University of Antwerp, Belgium.7.Department of Laboratory Medicine, Amsterdam UMC, Amsterdam, The Netherlands. 8.Department of Rheumatology and Clinical Immunology, Amsterdam UMC, location VUmc, Amsterdam, The Netherlands.9.Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands.10.Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands.

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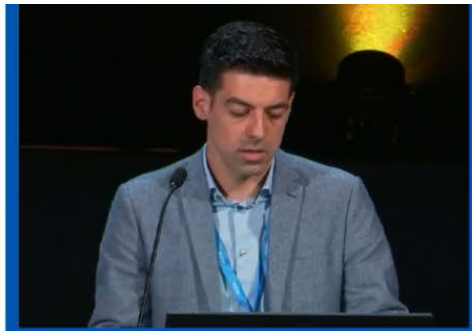

Luis Fernando Perez-Garcia

Lack of folylpolyglutamate synthetase activity and methotrexate polyglutamylation as underlying mechanisms explaining why methotrexate does not impair sperm quality.

OP0224

Lack of folylpolyglutamate synthetase activity and MTX polyglutamylation as underlying mechanisms explaining why MTX does not impair sperm quality

Luis Fernando Perez-Garica

Background

- iFAME-MTX: prospective cohort study

  Research question:

  Is MTX safe for men with immune mediated disease and active desire to becoma a father ?

  (Perez-Garcia LF, et al. Ann Rheum Dis 2023;0:1–8. doi:10.1136/ard-2023-224032)

- Previous presentation, EULAR 2022

  MTX **not** associated with testicular toxicity:

  - No sperm quality abnormalities
  - No sperm DNA damage
  - No reproductive endocrine axis abnormalities

OP0224

Lack of folylpolyglutamate synthetase activity and MTX polyglutamylation as underlying mechanisms explaining why MTX does not impair sperm quality

Luis Fernando Perez-Garica

Background

- iFAME-MTX: prospective cohort study

  Research question:

  Is MTX safe for men with immune mediated disease and active desire to become a father ?

  Perez-Garcia LF, et al. Ann Rheum Dis 2023;0:1–8. doi:10.1136/ard-2023-224032

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  MTX not associated with testicular toxicity:

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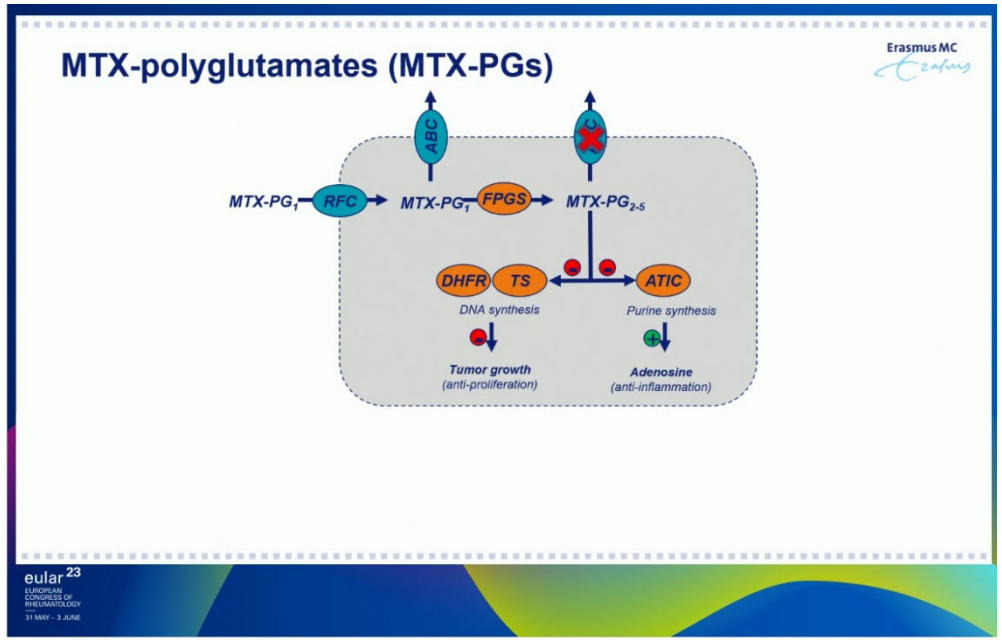
Lack of folylpolyglutamate synthetase activity and MTX polyglutamylation as underlying mechanisms explaining why MTX does not impair sperm quality

Luis Fernando Perez-Garica

Objective

To evaluate

- If MTX-PGs can be detected in spermatozoa of men exposed to MTX
- the FPGS enzymatic activity in spermatozoa



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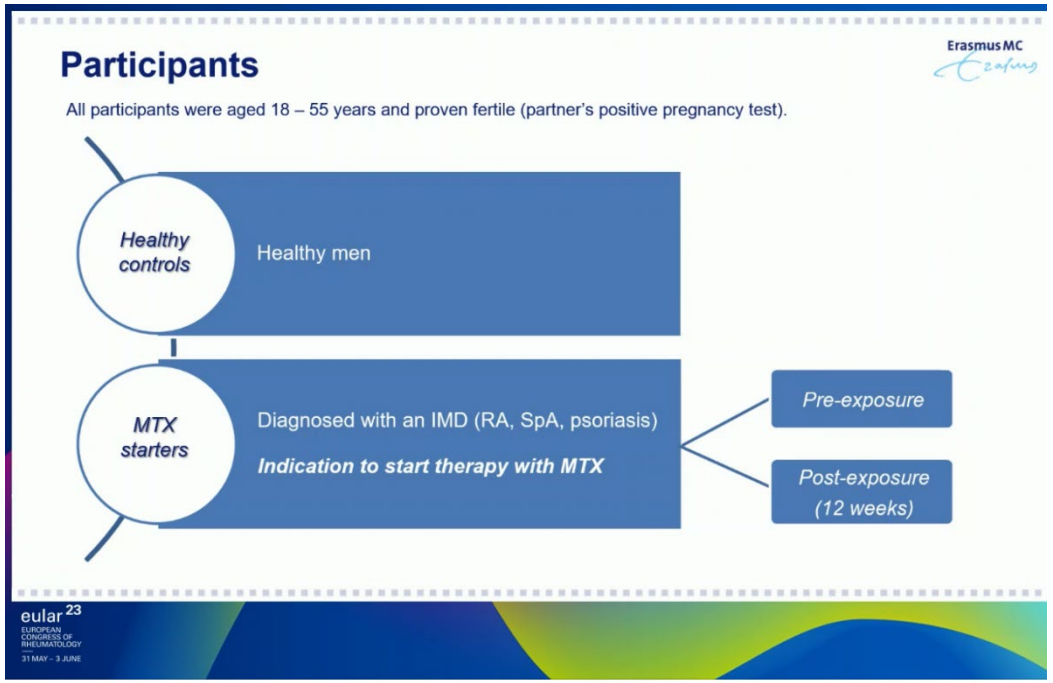

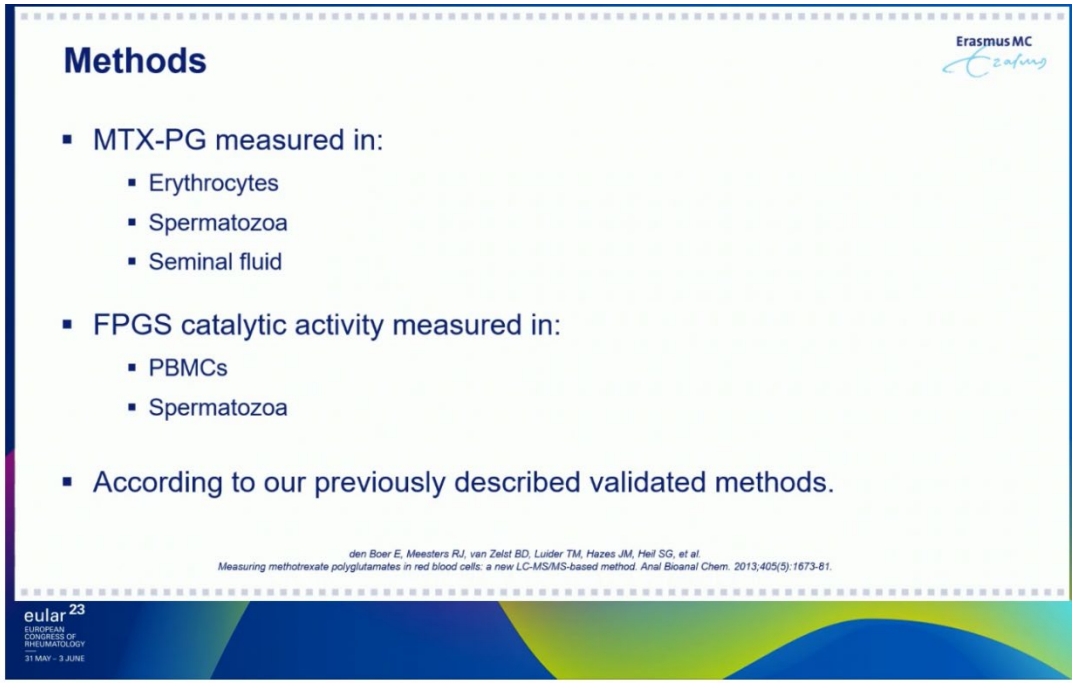

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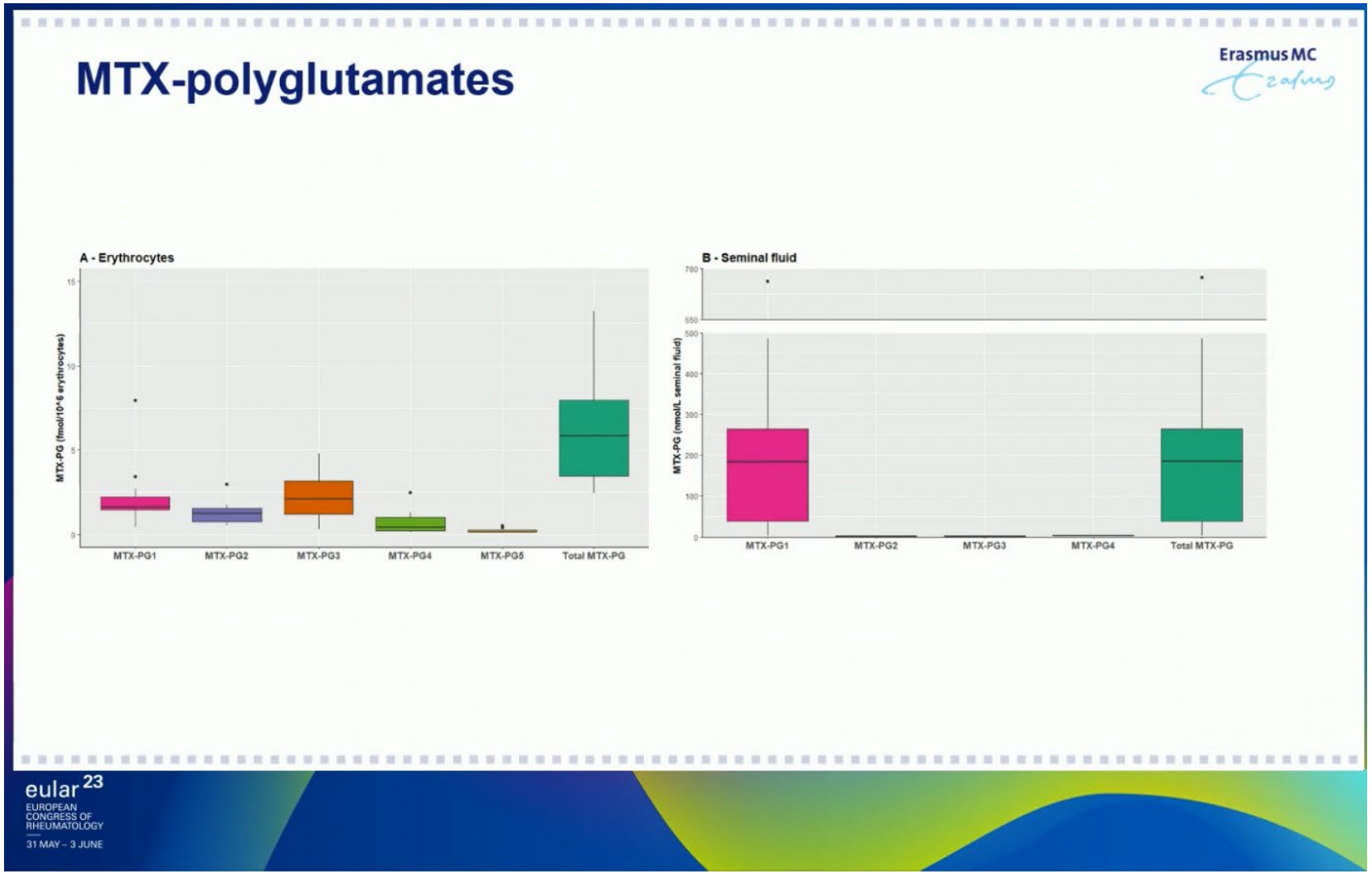

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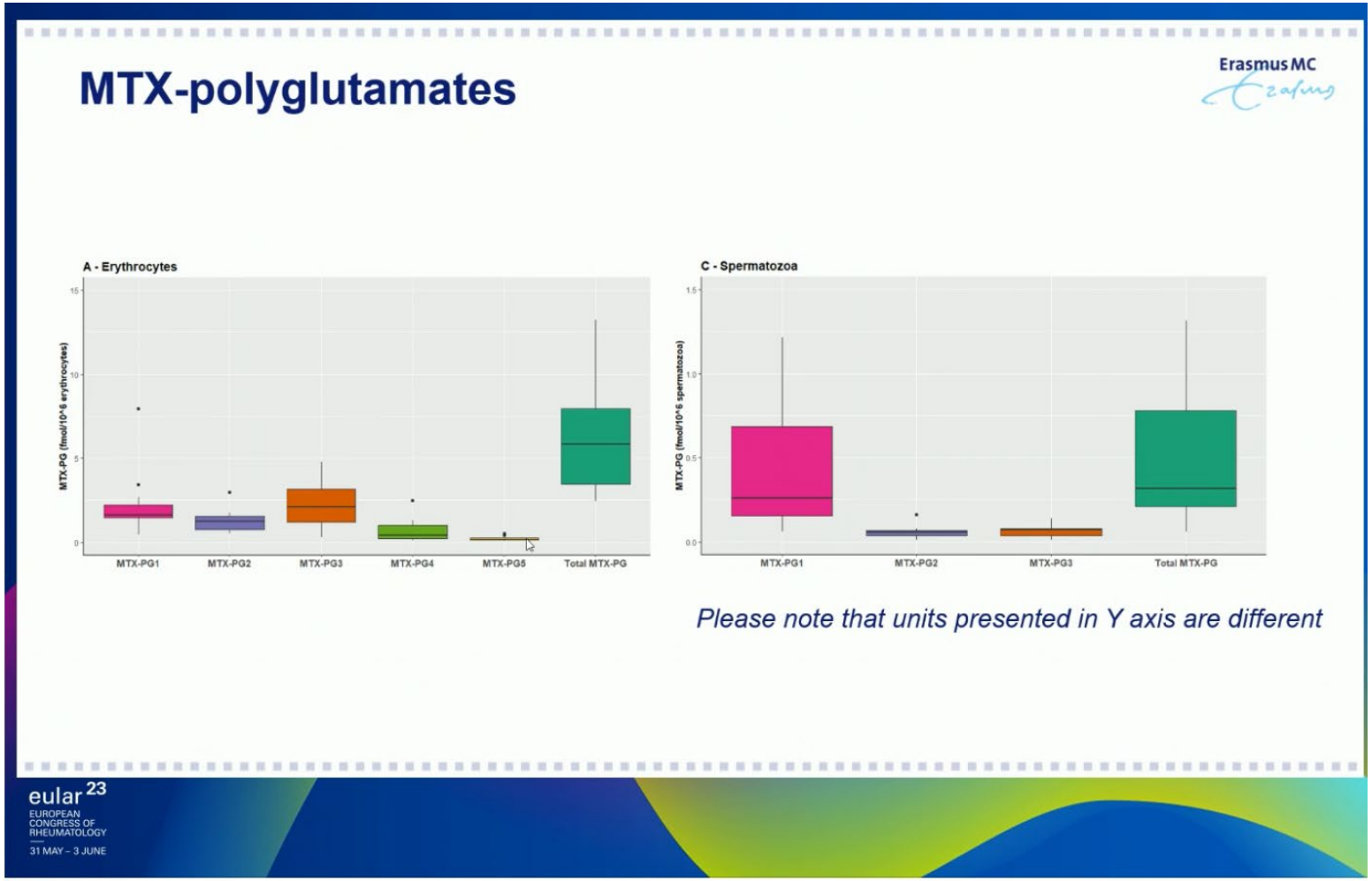

OP0224

Lack of folylpolyglutamate synthetase activity and MTX polyglutamylation as underlying mechanisms explaining why MTX does not impair sperm quality

Luis Fernando Perez-Garica

Conclusion

Erasmus MC

- Hardly any bioactive forms of MTX (MTX-PG) could be detected in spermatozoa.
- Spermatozoa have very low FPGS activity and hence lack the capacity to form MTX-PGs

Luis Fernando Perez-Garcia

Lack of folylpolyglutamate synthetase activity and methotrexate polyglutamylation as underlying mechanisms explaining why methotrexate does not impair sperm quality.

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31 MAY – 3 JUNE

TRANSLATIONAL SCIENCE

Is methotrexate safe for men with an immune-mediated inflammatory disease and an active desire to become a father? Results of a prospective cohort study (iFAME-MTX)

Luis Fernando Perez-Garcia ,[1] Esther Röder ,[1] Bouwe P Krijthe,[1,2] Laura JC Kranenburg-van Koppen,[1,3] Roxanne van Adrichem,[1] Els Zirkzee,[4] Pieter H Griffioen ,[5] Kris Peeters,[6] Marry Lin,[7] Eduard A Struys,[7] Gerrit Jansen,[8] Martijn BA van Doorn,[9] Robert de Jonge,[7] Gert R Dohle,[10] Radboud JEM Dolhain[1]

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Altogether, our data suggest that MTX is not associated with testicular toxicity. Therefore, therapy with MTX can be safely started or continued in men diagnosed with an IMID and with an active wish to become a father.

3) EULAR abstract about

Impact of hormone replacement treatment on functional status in RA

Why I chose this abstract?

- Compare results to our findings in SCQM cohort?

Impact of menopausal treatment on functional decline in women with RA

Sofia Pedro

Background and objectives

- Women with RA experience changes in disease development and progression surrounding reproductive and hormonal events, including menopause (Mollard et al. 2018).
- In our previous work, women with RA had better functional status prior to menopause and experienced a worse trajectory of functional decline after menopause
- Also, women were protected from functional decline with prior pregnancies, hormonal therapy and more reproductive years.

AIM: The purpose of this study is to investigate how menopausal treatments affect physical function decline in women with RA.

FORWARD
The National Databank for Rheumatic Diseases

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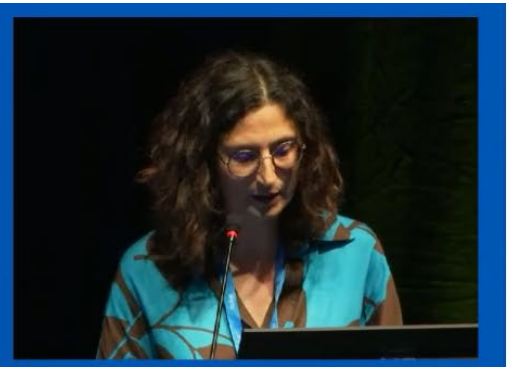
31 MAY – 3 JUNE

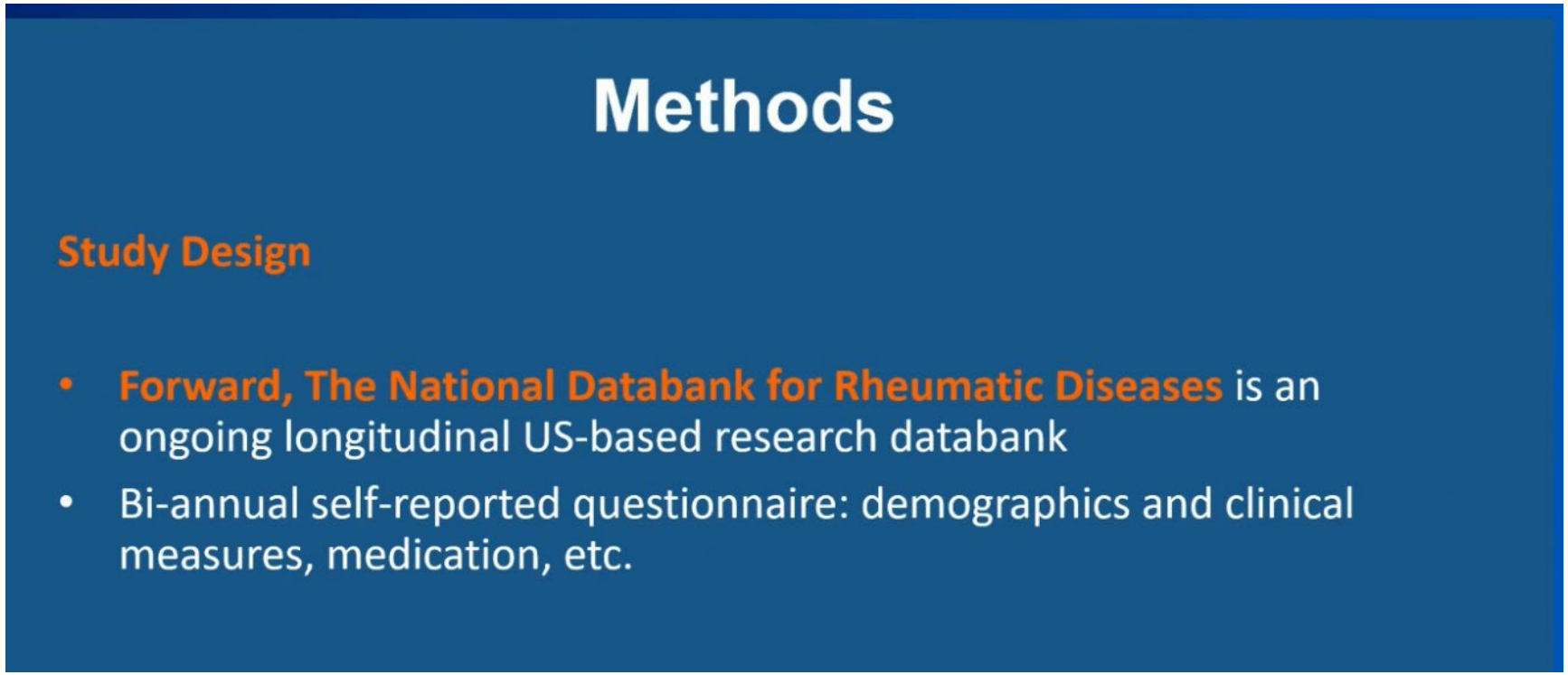


Sofia Pedro
Impact of menopausal treatments in functional decline on women with Rheumatoid Arthritis

OP0268

Impact of menopausal treatment on functional decline in women with RA

Sofia Pedro



OP0268

Impact of menopausal treatment on functional decline in women with RA

Sofia Pedro

Results - baseline characteristics

Reproductive history	Non-HRT users (n=4123)	HRT users (n=4123)	P-value
Age at menarche, years (n=7383)	12.7 (1.7)	12.6 (1.6)	0.265
Age at menopause, years (n=8215)	**45.8 (8.0)**	**43.1 (8.8)**	**0.000**
Length reproductive life, years (n=7383)	**33.1 (8.1)**	**30.4 (8.8)**	**0.000**
Ever pregnant, % (n=4270)	87.9 (1822)	88.2 (1928)	0.748
Number of pregnancies (n=3948)	**3.1 (1.9)**	**2.9 (1.7)**	**0.010**
Premature menopause (<40 years), %	**24.8 (1021)**	**38.5 (1587)**	**0.000**
HRT duration, years	--	2 (1-4)	
Median follow-up time, years (IQR)	6.5 (3.5 – 10.5)	5.5 (2.5 – 10.5)	0.000

OP0268

Impact of menopausal treatment on functional decline in women with RA

Sofia Pedro

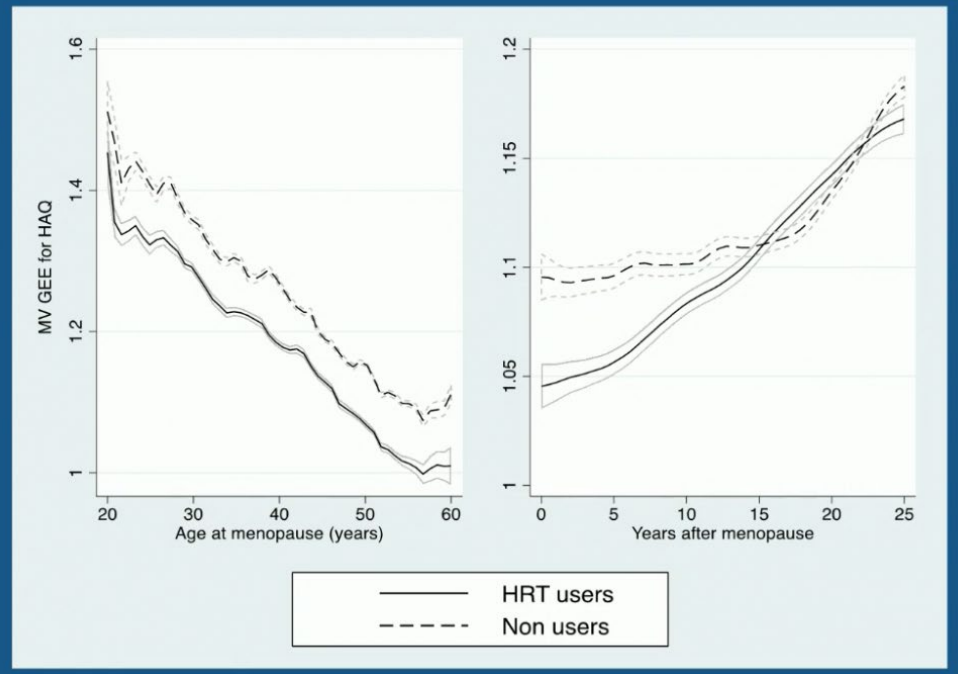
Results

GEE models

- **Best model:** age with 4-knot (48, 61, 70, & 83 years) cubic splines, Caucasian race, educational level, total income, employed, married, RA duration, smoking, alcohol use, BMI, RD comorbidity index, NTNF and non-hormonal treatment use, and age at menopause/years after menopause

- A modest association with HRT use and HAQ was found (β = -0.02, 95% CI -0.03, -0.01; P<0.001) with HRT users having consistently better HAQ compared to non-users
- HAQ was inversely associated with age of menopause (β = -0.008, 95% CI -0.03, -0.01; P<0.001)

Projections from MV GEE model



OP0268

Impact of menopausal treatment on functional decline in women with RA

Sofia Pedro

Conclusions

- HRT use was associated with better functional status, although of modest magnitude.
- Longer reproductive duration seemed protective for function (longer length of time from menarche to menopause).
- Function worsened slightly after menopause and premature menopause was associated with worse function.
- Future work is needed to assess other outcomes and the safety profile of HRT regarding incidence of malignancies, cardiovascular events, and osteoporosis in RA.

Sofia Pedro

Impact of menopausal treatments in functional decline on women with Rheumatoid Arthritis

RHEUMATOLOGY

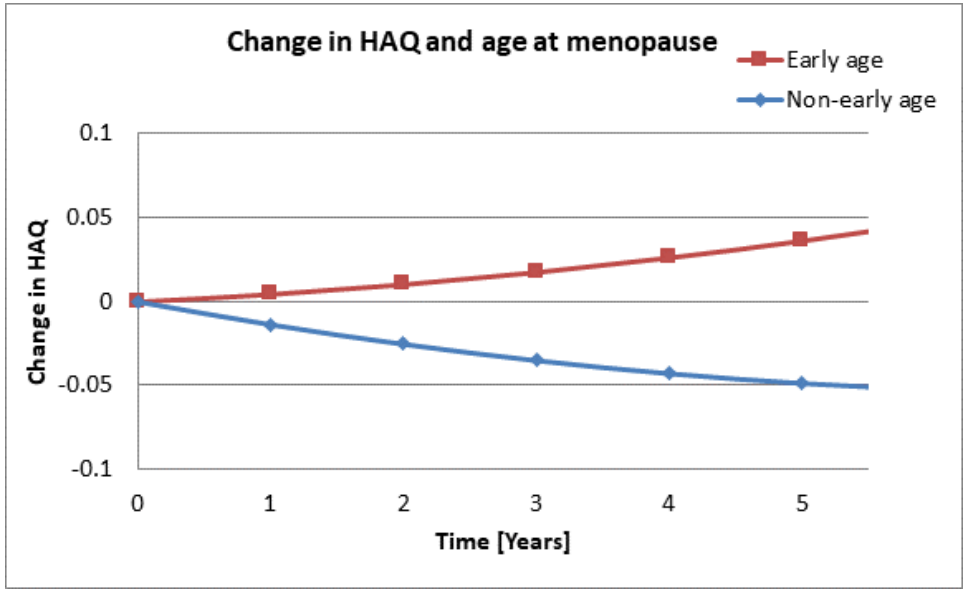
Rheumatology 2019;58:432–440
doi:10.1093/rheumatology/key311
Advance Access publication 31 October 2018

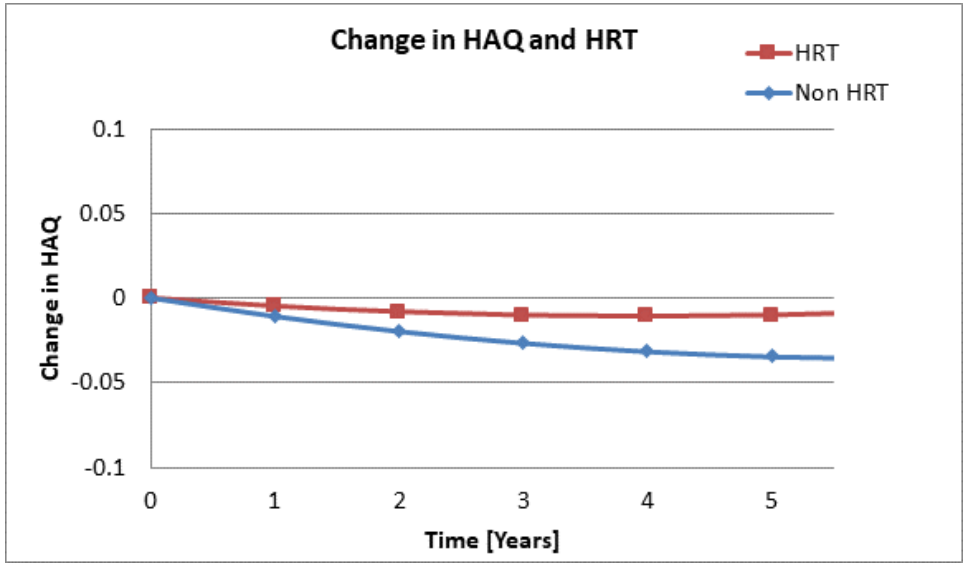
Original article

Role of reproductive and menopausal factors in functional and structural progression of rheumatoid arthritis: results from the SCQM cohort

Deshire Alpizar-Rodriguez[1], Frauke Förger[2], Delphine Sophie Courvoisier[1], Cem Gabay[1] and Axel Finckh[1] on behalf of the physicians of the Swiss Clinical Quality Management Program for Rheumatoid Arthritis

N=1667 women with RA analysed
1065 post-menopausal





RHEUMATOLOGY

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Rheumatology key messages

- Functional disability progresses more rapidly in post-menopausal than in pre-menopausal women with RA.
- RA patients with earlier age at menopause have a worse progression of functional disability.
- The more favourable function evolution during pre-menopause is not explained by age or disease duration.

4) EULAR abstract about
Hydroxychloroquine safety in pregnancy

Why I chose this abstract?

- Claims data: HCQ > 400 mg/d associated small increase in birth defects
  Huybrechts KTet al, Am J Obstet Gynecol 2021
- EMA recommends to update product information
- EULAR ReHFaP: „letter of concern" in response to EMA intention

POS1125 (2023)

HYDROXYCHLOROQUINE USE IN PREGNANT WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND MAJOR CONGENITAL MALFORMATIONS IN THE OFFSPRING

N. V. Nguyen[1], E. Svenungsson[2], A. Dominicus[3], K. Hellgren[1], J. Simard[4], E. Arkema[1]

Objective

- To assess the risk of major congenital malformations (MCM) associated with exposure to HCQ during the 1st trimester in the offspring of women with SLE.

Method

- Population-based cohort study with a singleton birth from 2006-2020

- National Patient Register Sweden: ICD code for SLE
- Prescribed Drug Register (dispensation): HCQ vs no-HCQ
- Medical Birth Register: Outcome -> ICD code for MCM in offspring, EUROCAT

- Propensity score model

POS1125 (2023)

HYDROXYCHLOROQUINE USE IN PREGNANT WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND MAJOR CONGENITAL MALFORMATIONS IN THE OFFSPRING

N. V. Nguyen[1], E. Svenungsson[2], A. Dominicus[3], K. Hellgren[1], J. Simard[4], E. Arkema[1]

Results

- 407 exposed births vs 520 unexposed births

- Risk of MCM

  HCQ-exposed 2.7% vs no-HCQ exposed 1.9%

  Unadjusted **RR 1.42 (95% CI 0.60-3.28)**
  Adjusted **RR 1.59 (95% CI 0.67-3.75)**

Conclusion

No statistically significant risk of MCM at birth among births born to women with SLE exposed to HCQ during the 1st trimester compared to those without HCQ exposure.

5) EULAR abstract about
TNFi in RA pregnancy and placental biomarkers

Why I chose this abstract?

- RA active - > low birth weight
- Recent data: TNFi use -> birth weight↑
- Biomarkers for Placental function: sFlt-1, PlGF

POS0631 (2023)

TNF INHIBITOR USE AFFECTS BIRTH WEIGHT INDEPENDENTLY OF THE SFLT-1/PLGF RATIO IN PREGNANT WOMEN WITH RHEUMATOID ARTHRITIS

C. Witte-Quaak[1], A. Kluivers[2], H. T. Smeele[3], R. I. Neuman[4], L. Saleh[2], A. H. J. Danser[4], R. Dolhain[3]

Background

- TNF inhibitor (TNFi) use during pregnancy is associated with increased birthweight of the offspring of women with Rheumatoid Arthritis (RA).

Objectives

- To study the modulating impact of sFlt-1 and PlGF on birthweight and the use of TNFi in a cohort of pregnant women with RA.

POS0631 (2023)

TNF INHIBITOR USE AFFECTS BIRTH WEIGHT INDEPENDENTLY OF THE SFLT-1/PLGF RATIO IN PREGNANT WOMEN WITH RHEUMATOID ARTHRITIS

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Methods

- Prospective PreCARA cohort, T2T
- Biomarkers at each trimester:
  sFLT-1 (soluble fms-like Tyrosine Kinase-1)
  PlGF (Placental growth factor)
  sFlt-1/PLGF

Results

- 158 women, 52% used TNFi (29.1% throughout pregnancy)
- sFlt-2/PlGF ratio was different in each trimester (1T 33, 2T 5, 3T: 3)
- No significant difference in sFlt-1 or sFlt-1/PlGF between TNFi users vs no-TNFi

  sFlt-1: β-0.000, 95% CI -0.063; 0.063 p = 0.997

  PlGF β -0.014, 95% CI -0.06; 0.093 p = 0.721

  sFlt-1/PlGF ratio: β-0.014, 95% CI -0.107; 0.078 p = 0.757

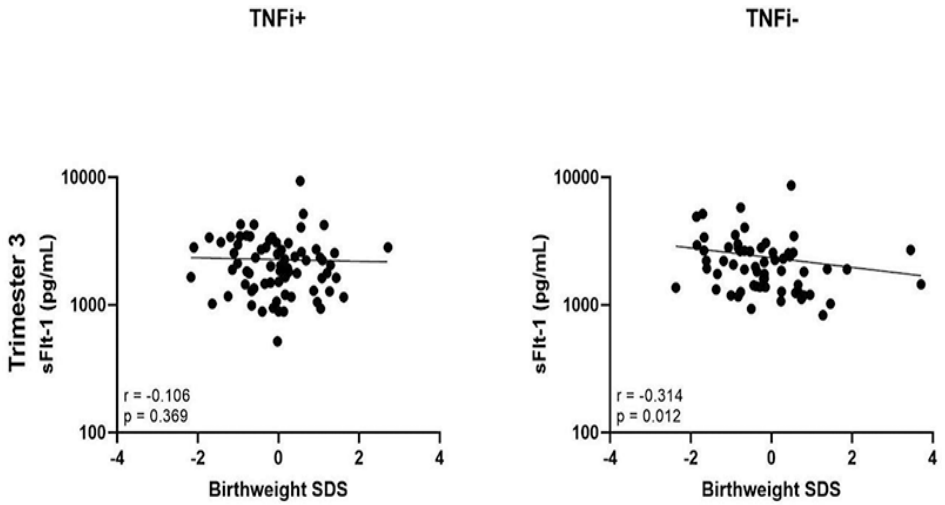
POS0631 (2023)

TNF INHIBITOR USE AFFECTS BIRTH WEIGHT INDEPENDENTLY OF THE SFLT-1/PLGF RATIO IN PREGNANT WOMEN WITH RHEUMATOID ARTHRITIS

C. Witte-Quaak[1], A. Kluivers[2], H. T. Smeele[3], R. I. Neuman[4], L. Saleh[2], A. H. J. Danser[4], R. Dolhain[3]

Results

Correlation : birthweight, sFlt-1



- Negative correlation of sFlt-1 on birthweight in patients not using TNFi disappeared in patients using TNFi.

Conclusions

-> TNFi improves birthweigt by antagonizing the effect of sFlt-1 on birthweight.

-> TNFi could be considered as therapeutic drug in clinical conditions associated with disturbed sFlt-1/PlGF

POS0719 (2023)

MATERNAL AND PERINATAL OUTCOMES IN WOMEN WITH VASCULITIS - A 13-YEAR EXPERIENCE FROM A PORTUGUESE TERTIARY CENTRE

A. R. Lopes[1,2], A. R. Cruz-Machado[1,2], S. C. Barreira[1,2], P. Martins[1,2], C. Araújo[3], M. Centeno[3], C. Ponte[1,2], L. Pinto[3], S. Capela[1,2]

Objectives

To describe maternal and perinatal outcomes in women with vasculitis

Methods

Observational retrospective study including pregnant women with vasculitis followed at a rheumatology-obstetric clinic from 01/2009 to 06/2022

POS0719 (2023)

MATERNAL AND PERINATAL OUTCOMES IN WOMEN WITH VASCULITIS - A 13-YEAR EXPERIENCE FROM A PORTUGUESE TERTIARY CENTRE

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Table 1. Maternal and perinatal outcomes in women with vasculitis followed at a rheumatology-obstetric clinic

Main diagnosis	N (%)	Gestational age at delivery (mean ± SD weeks)	BW (mean ± SD grams)	SGA N (%)	Miscarriages N (%)	FGR N (%)	Preterm births N (%)	Pregnancy flares N (%)	Post-partum flares N (%)
Behçet's disease	18 (58)	38.3 ± 1.5	3013± 494	4/14 (29)	1/18 (6)	0	3/17 (18)	4/17 (24)	4/14 (29)
Polyarteritis nodosa	4 (13)	37.4 ± 0.6	2783± 175	1/4 (25)	0	0	0	2/4 (50)	0
Takayasu arteritis	4 (13)	38.0 ± 2.1	2725± 364	1/4 (25)	0	1/4 (25)	1/4 (25)	1/4 (25)	1/4 (25)
IgA vasculitis	1 (3)	40.3	3435	0	0	0	0	0	0
ANCA-PR3 cutaneous vasculitis	1 (3)	40.9	2845	1	0	0	0	1	0
Relapsing polychondritis	1 (3)	36.0	2040	1	0	1	1	1	1
Cryoglobulinemic vasculitis	1 (3)	35.9	3020	0	0	0	0	0	0
Cryoglobulinemic vasculitis associated with Sjögren's syndrome	1 (3)	39.0	3000	0	0	0	0	0	0
	31 (100)	38.2 ± 2.1	2925± 566	**8/27 (30)**	1/31 (3)	2/31 (6)	**5/30 (17)**	9/25 (36)	6/27 (22)