samples were stimulated with 2ng/mL lipopolysaccharide (LPS) and the IL-6 and TNF- α cytokine concentrations were quantified at 24 hours. In addition, the epidermal growth factor (EGF), IFN- γ , IL-6, IP-10, MIP-1 α , and TNF- α levels were measured in 'pre-nVNS' serum and flow cytometric profiles of whole blood immune cells were analysed. The patient reported outcome measures (PROMs) recorded at each visit were the Visual Analogue Scale (VAS) (0-100cm) of abnormal fatigue, Hospital Anxiety and Depression (HAD) Scale, Orthostatic Grading Scale, Epworth Sleepiness Scale (daytime sleepiness), and Profile of fatigue (PRO-F) for Physical and Mental fatigue. Paired t-tests were performed to assess for changes in PROMs, cytokine levels, and cell subset distribution and associations of cytokine response with PROMs were investigated by correlation analyses.

Results: Eleven CFS, twelve FM and fourteen RA patients completed the study. There was a significant reduction in daytime sleepiness in CFS ($p = 0.0321$) and FM ($p = 0.0294$) patients between the final and baseline visits and a significant reduction in HAD depression ($p = 0.0413$) in FM (Fig.1). Improvement in VAS for abnormal fatigue, HAD-Anxiety, HAD-Depression, PRO-F Physical and Mental fatigue was observed in all three groups over the study period with a reduction in VAS fatigue in 64% of CFS, 67% of FM and 62% of RA patients. There were no significant changes in the immune cell subsets or in cytokine response. Finally, higher baseline pre-nVNS supernatant IL-6 levels were predictive of an improvement in VAS fatigue ($p = 0.0006$), Daytime Sleepiness ($p = 0.0466$) and PRO-F Physical fatigue ($p = 0.0196$) in RA, while higher baseline TNF- α levels were predictive of an improvement in VAS fatigue ($p = 0.0003$), Daytime Sleepiness ($p = 0.0380$), Orthostatic ($p = 0.0281$) and PRO-F Physical fatigue ($p = 0.0007$) in FM.

Conclusion: Our findings suggest that nVNS may contribute to the improvement of PROMs of fatigue in CFS, FM and RA. NVNS led to significant reductions in daytime sleepiness in CFS and FM, and depression in FM. Further studies and a larger sample size are needed to investigate the potential effects of nVNS on diseases characterised by persistent fatigue.

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Figure 1. VAS for abnormal fatigue and PROMs recorded at baseline and final visits in patients with chronic fatigue syndrome (CFS), fibromyalgia (FM) and rheumatoid arthritis (RA). Boxplots show the median, upper, and lower quartiles for PROMs at visit 1 and visit 3 in each disease group. Paired-t tests revealed a significant reduction in daytime sleepiness in CFS and FM (B), and a significant reduction in HAD depression in FM (E). Improvement trends were observed in VAS for abnormal fatigue, HAD-Anxiety, HAD-Depression, PRO-F Physical fatigue and PRO-F Mental fatigue in all three groups over the 26-day study period.

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INFLAMMATORY PROTEOMIC SIGNATURE RELATED TO DECREASED FERTILITY IN WOMEN WITH RHEUMATOID ARTHRITIS

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Background: Fertility issues are common in women with rheumatoid arthritis (RA). Decreased fertility in these patients is associated with high disease activity and the use of certain medication [1]. However, immunological mechanisms behind this phenomenon remain unresolved.

Objectives: This study aims to identify inflammation-related proteins associated with decreased fertility in women with rheumatoid arthritis and a wish to conceive.

Methods: Patients were derived from the PARA-study, a prospective cohort on RA and pregnancy. High-multiplex immunoassay technology with qPCR readout (Olink Proteomics, Uppsala, Sweden) was used to assess 92 inflammation-related proteins in serum obtained before pregnancy of 186 women with RA and a wish to conceive. Measured protein levels were imputed into multivariable cox regression models with time to pregnancy (TTP) as dependent variable. This model was corrected for known confounders age, nulliparity, NSAID use, prednisone use and past methotrexate use [2].

Results: Our analyses show prolonged TTP to be associated with increased expression of pro-inflammatory cytokines (TNF, IL-6, IL-18), chemokines (CCL23, CCL19, CXCL10, MCP-3, CXCL9) and T cell stimulating factors (TNFRSF9, CDCCP-1). Furthermore, increased factors associated with angiogenesis (VEGF-A) and bone and collagen damage (RANKL, MMP-1) were found. Lastly, decreased fertility is associated with increased immune regulatory factors (IL-10, IL10RB, PD-L1). After false discovery rate (FDR) correction for multiple testing, IL-10, CCL23, MCP-3 and CDCCP-1 remained statistically significant (adjusted $P < 0.05$). Results are depicted in table 1.

Conclusion: This study shows a pro-inflammatory proteomic signature, including a counterbalance of increased immune regulatory proteins, to be associated with prolonged TTP. These findings provide more insight into the immunological pathways involved in fertility in RA patients.

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Table 1. Significant multivariable cox regression results with time to pregnancy as dependent variable, corrected for age, nulliparity, NSAID use, prednisone use and past MTX use. HR = hazard ratio, FDR = false discovery rate.

Protein	HR	P	P FDR adjusted	Function
IL-10	0,64	0,001	0,026	Immune regulatory
CCL23	0,51	0,001	0,026	T cell/monocyte migration
MCP-3	0,74	0,001	0,026	Monocyte migration
CDCCP1	0,56	0,002	0,039	T cell migration
CCL19	0,77	0,005	0,077	DC/T cell/B cell migration
TNFRSF9	0,63	0,007	0,090	T cell costimulator
VEGF-A	0,7	0,014	0,154	Angiogenesis
CXCL10	0,82	0,021	0,185	T cell/monocyte/NK/DC migration
RANKL	0,76	0,022	0,185	Osteoclast activation, DC survival
IL-6	0,88	0,024	0,185	Pro-inflammatory cytokine, stimulation of acute phase response
PD-L1	0,55	0,027	0,189	Immune suppression
IL-18	0,7	0,035	0,193	Type 1 response activator
IL-7	0,69	0,038	0,208	Lymphocyte maturation
IL-10RB	0,48	0,039	0,208	IL-10 receptor
MMP-1	0,73	0,045	0,208	Collagen breakdown
TNF	0,44	0,048	0,208	Pro-inflammatory cytokine, necrosis
CXCL9	0,26	0,049	0,208	Th1 polarization

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