Keywords: Epidemiology, Pregnancy and reproduction, Inflammatory arthritides


Background: In the field of rheumatology, fertility has been reported impaired in Norwegian women with inflammatory joint diseases (IJDs) [1]. There is, however, limited data regarding fertility in male patients. The iFAME-fertility study found an association between inflammatory arthritis and reduced male fertility [2], underlining the need for a large-scale study. In the current project, we address this knowledge gap.

Objectives: 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.

Methods: We performed a nationwide, population-based cohort study. Male patients with IJDs (n = 10,865) collected from the Norwegian Arthritis Registry in 2021 were individually matched 1:5 on birth year, sex, and county of residence, with individuals without IJDs obtained from the National Population Register (n = 54,326). Data regarding births was obtained from the Medical Birth Registry of Norway. We compared the mean number of children per man in the patient group and in the comparison group using paired t-tests, and the proportion of childless men using Cochran–Mantel–Haenszel chi-squared tests.

Results: The mean number of children per man in the patient group was 1.80 versus 1.69 in the comparison group (p < 0.001). Altogether, 21% of our patients were childless vs 27% in the comparison group (p < 0.001, Figure 1). The difference in number of children between patients and comparison group was highest for those diagnosed after year 2000 and these patients had the comparatively lowest risk of being childless. The differences were less evident for those diagnosed before 2000 (Table 1). Age at diagnosis did not influence fertility (Table 1).

Conclusion: In this large nationwide study, fertility in male patients with IJDs was not reduced compared to controls, neither when examining the number of children per man, nor when looking at the proportion of childless men. Interestingly, we observed a higher fertility rate in male IJD patients than in the comparison group for patients diagnosed after year 2000. The reason for this observation is unknown. Factors associated with getting or having an IJD may influence fertility. An interesting hypothesis is a possible positive impact of new immune modulating drugs introduced after year 2000.

REFERENCES:

Table 1. Mean number of children and proportion of childless men according to time and age at diagnosis.

<table>
<thead>
<tr>
<th>Time at diagnosis</th>
<th>Age (years)</th>
<th>No. of children</th>
<th>Patients Comparisons</th>
<th>P-value</th>
<th>Childless men (%)</th>
<th>Patients Comparisons</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967 - 1985*</td>
<td>0 - 20</td>
<td>161</td>
<td>1.73</td>
<td>0.43</td>
<td>21.7</td>
<td>0.84</td>
<td>22.9</td>
</tr>
<tr>
<td></td>
<td>21 - 30</td>
<td>275</td>
<td>2.04</td>
<td>1.93</td>
<td>14.0</td>
<td>0.01</td>
<td>12.7</td>
</tr>
<tr>
<td></td>
<td>31 - 40</td>
<td>104</td>
<td>2.09</td>
<td>1.94</td>
<td>28.6</td>
<td>0.60</td>
<td>26.4</td>
</tr>
<tr>
<td>1986 - 1999</td>
<td>31 - 40</td>
<td>1360</td>
<td>1.83</td>
<td>1.83</td>
<td>19.0</td>
<td>0.84</td>
<td>21.9</td>
</tr>
<tr>
<td></td>
<td>0 - 20</td>
<td>118</td>
<td>1.58</td>
<td>1.52</td>
<td>0.65</td>
<td>0.56</td>
<td>28.0</td>
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<tr>
<td></td>
<td>21 - 30</td>
<td>415</td>
<td>1.72</td>
<td>1.72</td>
<td>0.91</td>
<td>0.09</td>
<td>22.2</td>
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<td>382</td>
<td>1.96</td>
<td>1.96</td>
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<td>41 - 50</td>
<td>323</td>
<td>1.98</td>
<td>1.96</td>
<td>0.79</td>
<td>0.22</td>
<td>13.9</td>
</tr>
<tr>
<td>2000 - 2021</td>
<td>0 - 20</td>
<td>173</td>
<td>1.46</td>
<td>1.46</td>
<td>1.00</td>
<td>0.91</td>
<td>73.4</td>
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<tr>
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<td>1069</td>
<td>1.05</td>
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<td>&lt;0.001</td>
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<tr>
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<td>&lt;0.001</td>
<td>22.8</td>
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<tr>
<td></td>
<td>41 - 50</td>
<td>1999</td>
<td>1.92</td>
<td>1.77</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>17.4</td>
</tr>
</tbody>
</table>

* The Medical Birth Registry contains information about all births in Norway since 1967, and children born before this are not registered. This gives a lower mean no. of children per man, mainly affecting men 41 – 50 years of age in the 1967 - 1985 era.

Figure 1. Proportion of childless men. Treatment era reflect major changes in treatment strategy for the IJDs – methotrexate from the late 1980s and biological treatment from the early 2000s.

Acknowledgements: NIL.
Inflammatory Rheumatic Diseases Have a Broad Impact on Reproductive Health – A Nationwide Evaluation and Systematic Comparison Across Rheumatic Diseases

Keywords: Pregnancy and reproduction

N. Mars1,2, A. Kerola3, K. Eklund4,5, H. Laivuori1,6, S. Ripatti1,2,7, A. Palomäki1,8, F. Registry1,9, University of Helsinki, Institute for Molecular Medicine Finland, FIMM, HI-LIFE, Helsinki, Finland; Broad Institute of MIT and Harvard, Cambridge, United States of America; Helsinki University Hospital, Inflammation Center, Rheumatology, Helsinki, Finland; University of Helsinki and Helsinki University Hospital, Department of Rheumatology, Helsinki, Finland; Orton Orthopaedic Hospital, Helsinki, Finland; Tampere University Hospital and Tampere University, Faculty of Medicine and Health Technology, Department of Obstetrics and Gynecology, Tape, Finland; University of Helsinki, Department of Public Health, Helsinki, Finland; Turku University Hospital and University of Turku, Centre for Rheumatology and Clinical Immunology, and Department of Medicine, Turku, Finland; Finnish Institute for Health and Welfare, Helsinki, Finland

Background: Inflammatory rheumatic diseases (IRDs) affect men and women of reproductive age. The lack of reproductive health studies on IRDs hinders making evidence-based recommendations on fertility preservation, prevention of pregnancy complications, and management of the IRDs during reproductive years.

Objectives: To systematically estimate the impact of IRDs on diverse reproductive outcomes and compare the effects to those observed for other immune-mediated inflammatory diseases.

Methods: The total Finnish population (FinRegistry: N=5,339,804) was linked to nationwide registries (inpatient and outpatient care, and Medical Birth Register covering all live births since 1987; N=1,920,411 births). We focused on seroserogetic and seronegative rheumatoid arthritis (RA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), and Sjögren syndrome (SS), selecting individuals born 1964–1984 diagnosed with the IRD before age 30, and 20 sex, birth-year, and education level-matched controls. The patterns were compared to a range of other immune-mediated inflammatory diseases, such as type 1 diabetes, inflammatory bowel disease, and hypothyroidism.

Results: The case count of women with an IRD ranged from 412 for PsA to 1,487 for seroserogetic RA (mean age range at diagnosis 11.0 in JIA to 25.7 in AS). Women with IRD experienced a higher prevalence of childlessness than controls (mean difference 4.2%, largest in JIA at 9.3%), had fewer children (mean 0.2 fewer; highest in JIA at 0.3 fewer), and the start and end of reproduction were slightly shifted towards an earlier age. Also men with IRD experienced a higher prevalence of childlessness than controls (mean difference 4.1%, largest in SLE at 11.0%). Overall, the impact was similar in other immune-mediated inflammatory diseases in both women and men, with high variability between diseases. For maternal health conditions, five IRDs showed an elevated risk for pre-eclampsia, with the largest effect size observed for SLE (OR 2.65, 95%CI 1.94–3.62). No elevated risk was observed for gestational diabetes in any of the IRDs. Many of the IRDs were associated with at least one of the ten evaluated adverse perinatal outcomes, such as risk of non elective Caesarean section, and admission to neonatal ICU (Figure 1), with the largest effect sizes observed for SLE and SS.

Conclusion: In this comprehensive, nationwide evaluation of reproductive health metrics, we observed widespread impact of IRDs on reproductive health. The effects were comparable to many other immune-mediated inflammatory diseases, but we also observed high variability between diseases. Overall, these findings emphasize the need for further research, and the importance of counseling on reproductive health in both men and women with IRDs.

Disclosure of Interests: None Declared.

Acknowledgements: NIL.

REFERENCES: NIL.

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Figure 1. Systematical analysis of perinatal outcomes, with results shown for three of the ten evaluated perinatal outcomes. Results are shown for diseases with over 20 cases for the outcome and associations with p-value >0.05 are shown in gray. NICU = neonatal ICU, ITP = immune thrombocytopenic purpura.

Cost-utility of a Progressive Spacing of Tocilizumab or Abatacept in Patients with Rheumatoid Arthritis in Sustained Remission: A MEDICO-ECONOMIC ANALYSIS OF THE TOLEDO TRIAL

Keywords: Clinical trials, bDMARD, Rheumatoid arthritis

J. Kedra1,2, B. Granger1,3, L. EL Houari1,3, F. Tubach1,3, B. Fautrel1,2, Sorbonne Université, INSERM UMR 1136, Institut Pierre Louis d’ Epidemiologie et de Santé Publique, Paris, France; AP-HP, Hôpital Pitié Salpêtrière, Rheumatology, Paris, France; AP-HP, Hôpital Pitié Salpêtrière, Département de Santé Publique, Centre de Pharmacopédiologie (Cephepi), CIC-190, Paris, France

Background: Biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDs) progressive tapering is a real opportunity in people living with rheumatoid arthritis (RA) having achieved remission both from the patient and the Society perspectives. The ToLEDo (Towards the Lowest Efficacious Dose) trial aimed to assess a disease activity-driven progressive tapering strategy of tocilizumab (TCZ) or abatacept (ABA) compared to their maintenance at full dose in RA patients in sustained remission. Non-inferiority (NI) was not demonstrated in terms of disease activity (primary endpoint) nor relapses, major relapses, radiographic progression (secondary endpoints) [1].

Objectives: The aim of this secondary analysis was to assess the cost-utility of the spacing strategy (S-arm) in the ToLEDo trial compared to full dose maintenance (M-arm).

Methods: The ToLEDo trial is a multicenter 2-year NI randomized open-label controlled trial, which enrolled 228 patients (113 in the S-arm and 115 in the M-arm). A cost-utility analysis was conducted on the per protocol population. In each arm, health benefits were estimated every 6 months by Short Form Health Survey (SF-6D) and EuroQol (EQ-5D) derived utility measurements. Cost elicitation integrated health resource use including bDMARD costs (direct cost) as well as productivity loss (indirect cost) using the friction cost method. The incremental cost-utility ratios (ICUR) were calculated by dividing the difference of costs between S-arm and M-arm by the difference of utilities between the 2 arms. 95% confidence interval (95%CI) were calculated by bootstrap (20,000 iterations). The incremental net benefit (INB) was calculated for willingness to pay (WTP) values ranging from 0 to 150,000€. The analyses were replicated using SF-6D (primary analysis) or EQ-5D, and in ABA and TCZ subgroups. Acceptability analyses as well as stochastic sensitivity analyses (simulating costs and utilities using MCMC algorithms) were also performed.

Results: Overall, 178 patients were included (82 in S-arm, 96 in M-arm) in the per protocol analysis. At the end of the follow-up in the S-arm, 15.0% of patients discontinued their biologic, 48.7% spaced the injections, and 39.3% remained at the standard dose. The difference in terms of two-years utility gains between S-arm and M-arm was 0.004 (95%CI -0.012, 0.021) with SF-6D. The difference in terms of disease activity-driven progressive tapering strategy of tocilizumab (ToLEDo): Results of a Multicenter Non-Inferiority Randomized Open-Label Controlled Trial Assessing Tocilizumab or Abatacept Injection Spacing in Rheumatoid Arthritis Patients in Remission [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10).