Burden of comorbidities and medication use in childbearing women with rheumatic diseases: a nationwide population-based study

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Subjects
Korean women with rheumatic diseases (RDS) during their childbearing years

Aim
Prevalence of comorbidities and medication use

Method
NHIS-NHID database

Results
Women of childbearing age with RDS

| Comorbidities          | (than controls) | Medication use     | (than controls) |
|------------------------|-----------------|--------------------|-----------------|
| Overall                | X 3.0           | NSAID              | X 13.8          |
| Hypertension           | X 2.9           | Corticosteroids    | X 68.2          |
| Hypertension           | X 2.8           |                    |                 |
| Diabetes mellitus      | X 1.4           |                    |                 |
| Cancer                 | X 1.3           |                    |                 |

Conclusion
Korean women with RDS have a greater burden of comorbidities and medication use during their childbearing years than women without RDs of the same age.

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INTRODUCTION

Rheumatic diseases (RDs) such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS) can affect women during their reproductive years [1-3]. As RDs are chronic inflammatory diseases requiring life-long management, disease- and treatment-related complications and various comorbidities associated with these diseases can significantly affect childbearing in women with RDs. The influence of disease activity on pregnancy outcomes in patients with RDs has been well documented. High disease activity has been shown to be associated with adverse pregnancy outcomes in patients with SLE, RA, and AS [4-6]. Moreover, medications used for disease control can affect fertility and pregnancy outcomes. Treatment with cyclophosphamide can result in permanent ovarian failure [7]. Exposure to methotrexate (MTX) and mycophenolate mofetil (MMF) have been consistently reported to increase the rate of miscarriage. However, whether there is a correlation between miscarriages and drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids (CSs), cyclophosphamide, cyclosporine, and tacrolimus remain unclear because these drugs are used in combination therapy; thus, conclusions cannot be drawn regarding single-drug exposure [8]. In addition, various comorbidities can affect childbearing in patients with RDs. Cardiovascular disease (CVD) and cancer are known to be more prevalent in patients with RA, AS, and SLE than in the general population [9-11]. However, the effects of comorbidities associated with RDs on childbearing or pregnancy outcomes have not been studied. From the studies showing increased rates of obstetric and fetal complications in women with CVD [12], and decreased fertility and permanent ovarian failure in premenopausal women being treated for cancer [13], we can infer that women in childbearing age with RDs are at risk for infertility and adverse pregnancy outcomes.

Although the burden of the disease on women of childbearing age has been studied previously [14-16], few studies have evaluated the burden of comorbidities and treatment medications used by women with RDs during their childbearing years. Determining the nationwide prevalence of comorbidities and medication use in a specific age group of women of childbearing age with RDs may provide valuable information for understanding the socioeconomic burden imposed on this specific population group. Thus, we aimed to estimate the prevalence of comorbidities and medication use among Korean women with RDs in their childbearing years using a nationwide population database. In this study, we focused on two important comorbidities, namely CVD and cancer. To assess the CVD risk, we assessed the prev-
alence of hypertension (HTN), diabetes mellitus (DM), and hyperlipidemia (HLD), which are traditional risk factors for CVD.

METHODS

Study design and source population

We conducted a retrospective cohort study using data from the Korean National Health Insurance Service-National Health Information Database (NHIS-NHID) from 2009 to 2016. The Korean NHIS is a single insurer that provides coverage for almost the entire Korean population; 97% of the Korean population is enrolled in the NHIS program [17]. As of December 2014, the NHIS database included all inpatient and outpatient claims data and information of approximately 50 million Korean people [18]. The NHIS-NHID has four databases with collected data on participants’ insurance eligibility, medical treatment, medical care institution, and general health examinations [18]. This study included women of childbearing age (defined as women between the ages of 20 and 44 years) whose data had been collected during the period from January 1, 2009, to December 31, 2016. This study was approved by the Institutional Review Board of the National Health Insurance Service Ilsan Hospital (Institutional Review Board number: NHIMC 2020-06-011) and conducted according to the principles of the Declaration of Helsinki. As the database used in this study contains anonymized data for research purposes, informed consent was not required.

Study population

The study population included a cohort of cases and controls. Cases included in the RD group were women from the NHIS-NHID with seropositive RA, SLE, and AS between the ages of 20 and 44 years identified with the diagnostic codes of M05, M32, and M45 based on the International Classification of Diseases (ICD), 10th revision code, during the study period. RA, SLE, and AS were selected as they are representative RDs that occur frequently in women of reproductive age. In 2009, the government of the Republic of Korea subsidized medical expenses for patients with rare and intractable diseases through a copayment assistance policy called the Individual Copayment Beneficiaries Program (ICBP), and seropositive RA, SLE, and AS were designated as the rare diseases covered by this program. Under this ICBP system, the NHIS established a registration program that includes codes for the target disease classified per the Korean Standard Classification of Diseases (KCD)-7 (based on the ICD-10), date of definitive diagnosis, and tests performed for the confirmation of the diagnosis. We used data from January 1, 2009, with the assumption that all patients with seropositive RA, SLE, and AS have been accurately coded since ICBP registration requires fulfillment of classification criteria for definitive diagnosis.

Control subjects were age-matched women without diagnostic codes for seropositive RA (M05), SLE (M32), or AS (M45) designated in the NHIS-NHID during the study period; they were randomly sampled in a 1:5 ratio. Control subjects were given an index date that was the same as the date of diagnosis of the matched cases.

Outcome measures

Four specific comorbidities chosen for prevalence estimation were HTN, HLD, DM, and cancer. Comorbidities were identified using ICD-10 codes (I10-12/15 for HTN, E78 for HLD, E10-14 for DM, and C* for cancer). As cancer was one of the four major conditions eligible for insurance coverage benefits with a registration requirement to receive the benefit, it was assumed to be accurately coded [19]. In the RD group, only comorbidities occurring after the date of definitive diagnosis of RD were included. Likewise, comorbidities occurring after the index date were included in the control subjects. Frequently prescribed medications for RDs, including NSAIDs, Cs, and disease-modifying anti-rheumatic drugs (DMARDs), were chosen to estimate their use. DMARDs included in the analysis were azathioprine, cyclosporine, hydroxychloroquine, sulfasalazine, tacrolimus, MTX, leflunomide, MMF, mizoribine, etanercept, golimumab, infliximab, ustekinumab, abatacept, and tocilizumab. Prescribed medications were identified based on the generic names of the drugs from the medical treatment database, and medications consecutively prescribed for over 90 days were assessed. Topical Cs were excluded from the analysis.

Statistical analysis

A descriptive analysis was performed to summarize the baseline characteristics of the participants. Categorical variables are presented as frequencies and percentages, and continuous variables are presented as mean with standard deviation (SD). To compare the prevalence of comorbidities
between the RD and control groups, the chi-square test was used, and odds ratios (ORs) with 95% confidence intervals (CIs) were adjusted for age, income level, and residential district. A \( p < 0.05 \) was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

**RESULTS**

**Characteristics of the study population**
A total of 41,547 women with RDs and 208,941 controls, both of childbearing age were identified. The RD group included 23,756 (57.2%) women with RA; 12,756 (30.47%) women with SLE; and 5,035 (12.1%) women with AS. The demographic characteristics of subjects with RDs and controls are shown in Table 1. The mean ± SD age was 35.0 ± 6.5 years in both the RD and control groups. More women in the RD group than in the control group were enrolled in medical aid, had lower income level, and had their residence in a special city district.

**Prevalence of comorbidities**
Table 2 shows the prevalence of comorbidities, i.e., HTN, HLD, DM, and cancer, among women with RDs and control subjects of childbearing age. The prevalence of all four measured comorbidities was significantly higher in the RD group than in the control group (\( p < 0.0001 \) for all). Women of childbearing age with RDs were more likely to have at least one of the measured comorbidities (OR, 3.0; 95% CI, 2.9 to 3.1). Likewise, the RD group was more likely to have HTN (OR, 2.9; 95% CI, 2.8 to 3.0), HLD (OR, 2.8; 95% CI, 2.7 to 2.9), DM (OR, 1.4; 95% CI, 1.4 to 1.5), and cancer (OR, 1.3; 95% CI, 1.3 to 1.4) than the age-matched controls.

When the prevalence of comorbidities was compared between the women with different RDs, significant differences were found among the RD groups. SLE had the highest prevalence of all four comorbidities followed by RA and AS (Fig. 1). ORs for having at least one of the measured comorbidities were 5.4 (95% CI, 5.2 to 5.7) for SLE, 2.3 (95% CI, 2.1 to 2.5) for RA, and 1.3 (95% CI, 1.2 to 1.4) for AS.

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**Table 1. Baseline characteristics of study population: RDs and controls**

| Characteristic         | RDs (n = 41,547) | Controls (n = 208,941) | \( p \) value |
|------------------------|------------------|------------------------|---------------|
| Age, yr                | 35.0 ± 6.5       | 35.0 ± 6.5             | -             |
| 20–24                  | 3,387 (8.2)      | 17,073 (8.17)          |               |
| 25–29                  | 6,050 (14.6)     | 30,466 (14.6)          |               |
| 30–34                  | 7,877 (19.0)     | 39,649 (19.0)          |               |
| 35–39                  | 11,457 (27.6)    | 57,579 (27.6)          |               |
| 40–44                  | 12,776 (30.8)    | 64,174 (30.7)          |               |
| Income level<sup>a</sup> |                  |                       | <0.001        |
| < 3                    | 12,869 (31.0)    | 69,408 (34.4)          |               |
| 3–7                    | 16,853 (40.6)    | 87,833 (43.5)          |               |
| > 7                    | 9,092 (21.9)     | 44,724 (22.1)          |               |
| Insurance              |                  |                       | <0.001        |
| Employee               | 25,791 (62.9)    | 129,338 (61.9)         |               |
| Self-employment        | 13,635 (33.2)    | 75,563 (36.2)          |               |
| Medical aid            | 1,602 (3.9)      | 4,040 (1.9)            |               |
| Residential district   |                  |                       | <0.001        |
| City, province         | 8,951 (21.5)     | 46,642 (22.3)          |               |
| Metropolitan city      | 10,490 (25.3)    | 53,465 (25.6)          |               |
| Special city           | 6,725 (25.7)     | 108,834 (52.1)         |               |

Values are presented as mean ± SD or number (%). RD, rheumatic disease.
<sup>a</sup>Income levels are presented by decile method (group > 7 refers to low-income group).
The prevalence of comorbidities in women of childbearing age (20 to 44 years) with and without RDs is presented in Table 2. Women with SLE had the highest odds of having HTN (OR, 8.0; 95% CI, 7.7 to 8.4), HLD (OR, 3.6; 95% CI, 3.5 to 3.7), DM (OR, 1.9; 95% CI, 1.7 to 2.1), and cancer (OR, 1.7; 95% CI, 1.5 to 1.9) compared to controls. Medication use was prevalent among women with RDs, with NSAIDs being prescribed in 81.6% of patients with RDs. Almost all (97.9%) women of childbearing age with RDs were taking RD-related medications. RA, SLE, AS, DMARDs, and NSAIDs were also compared in Figure 1 and Figure 2.
Table 3. Medication use in women of childbearing age (20 to 44 years) with and without RD

| Variable | Controls (n = 208,941) | RDs<sup>a</sup> (n = 41,547) | RA (n = 23,756) | SLE (n = 12,756) | AS (n = 5,035) |
|----------|------------------------|-------------------------------|-----------------|-----------------|--------------|
|          | No. (%) | OR<sup>b</sup> (95% CI) | No. (%) | OR<sup>b</sup> (95% CI) | No. (%) | OR<sup>b</sup> (95% CI) | No. (%) | OR<sup>b</sup> (95% CI) |
| NSAIDs   | 54,596 (26.1) | 33,909 (81.6)<sup>c</sup> | 22,380 (94.2)<sup>c</sup> | 6,839 (53.6)<sup>c</sup> | 11,353 (89.0)<sup>c</sup> | 4,690 (93.2)<sup>c</sup> | 50.6 (45.1−56.7) |
| CSs      | 10,689 (5.1)  | 32,338 (77.8)<sup>c</sup> | 19,871 (83.7)<sup>c</sup> | 10,333 (81.0)<sup>c</sup> | 2,134 (42.4)<sup>c</sup> | 2,134 (42.4)<sup>c</sup> | 15.5 (14.5−16.4) |
| DMARDs   | 1,181 (0.6)   | 36,275 (87.3)<sup>c</sup> | -           | 21,700 (91.3)<sup>c</sup> | -           | 3,222 (64.0)<sup>c</sup> | -        |

RD, rheumatic disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; AS, ankylosing spondylitis; OR, odds ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; CS, corticosteroid; DMARD, disease modifying anti-rheumatic disease.

<sup>a</sup>RDs include RA, SLE, and AS.

<sup>b</sup>Adjusted for age, income level, and residential district.

<sup>c</sup>p < 0.0001 compared with controls.

DISCUSSION

This study demonstrates that Korean women of childbearing age with RDs had a higher prevalence of comorbidities, including HTN, HLD, DM, and cancer, and had a higher burden of medication use than the general population of the same age and sex. Women of childbearing age with RDs were three times more likely to have at least one comorbidity, such as HTN, HLD, DM, or cancer, and had a higher risk of developing the comorbidity than age-matched control subjects in this study. This result is expected because control subjects in this study had a known increased risk of CVD and cancer compared with the general population. The prevalence of HTN, HLD, DM, and cancer was increased by 48% in patients with RA compared with the general population [8,9,10]. The risk of developing HTN, HLD, DM, or cancer, and cancer compared with the general population was increased by an OR of 1.16 (95% CI, 1.13 to 1.19) in patients with RA [9]. The CVD risk for patients with RA was 2 to 50 times greater than the risk for the general population. Therefore, the combined effects of non-traditional risk factors (e.g., inflammation, autotools, functional disability) and traditional risk factors (e.g., HTN, HLD, DM, obesity, and smoking) for the general population was 2 to 50 times greater than the risk for patients with RA [9]. The prevalence of HTN, HLD, DM, and cancer was also higher in patients with AS compared with the general population. The prevalence of HTN, HLD, DM, and cancer was 2.48 times greater than the risk for patients with AS [9]. The CVD risk for patients with AS was 2.48 times greater than the risk for patients with AS [9]. The prevalence of HTN, HLD, DM, and cancer was 2 to 50 times greater than the risk for patients with AS [9]. The CVD risk for patients with AS was 2 to 50 times greater than the risk for patients with AS [9].
Increased overall cancer risk has been demonstrated in patients with SLE (standardized incidence ratio [SIR], 1.28) [26], and AS (hazard ratio [HR], 1.38) [27] compared with those without the disease. In addition, a 10% increase in overall malignancy risk was shown in patients with RA compared with control subjects [28]. Our findings of increased prevalence of HTN, HLD, DM, and cancer in women of childbearing age with RDs compared with control subjects are comparable to those of previous studies exploring CVD and cancer risk in patients of all ages with RDs.

A notable finding of our study is that relatively young women in their childbearing years had an increased likelihood of having a comorbidity such as HTN, HLD, DM, or cancer. This is in contrast to findings in the general population that the risks of CVD and cancer are higher in men than in women and increase with age [29,30]. Although no previous study has evaluated the prevalence of comorbidities in the specific population of women of childbearing age, the risk ages for CVD and cancer were reported to be younger in patients with RDs than in the general population. In RA, the relative risk (RR) for CVD was highest in patients younger than 50 years (RR, 2.59), whereas patients older than 65 years showed the lowest RR of 1.27 compared with the general population [31]. Patients with SLE younger than 40 years had the highest RR for CVD in a retrospective cohort study performed in the UK [32]. In patients with AS, the risk of ischemic heart disease was higher in the newly diagnosed younger age group [33]. Patients younger than 45 years showed greatest SIR (4.11) for cancer in a study of patients with SLE [34], and a similar trend was reported in patients with AS [35].

We cannot explain the increased prevalence of several comorbidities among women with RDs during their childbearing years without evaluating the effect of medication. Several medications used to treat RDs have been shown to promote the development of CVD and cancer. Continuous use of NSAIDs has been demonstrated to increase the incidence of HTN and risk of CVD [36,37]. Use of CSs also increases CVD risk due to their detrimental effects on lipids, glucose tolerance, and HTN [38,39], and higher cumulative doses of CSs are related to the development of lymphoma in patients with SLE (HR, 1.94; 95% CI, 1.11 to 3.39) [40]. Some DMARDs such as cyclosporin and azathioprine, have also been associated with an increased risk of malignancy [41]. In addition, medications used to treat RDs can result in reduced fertility [42]. Although the risk is low, NSAIDs can impair fertility [43], and immunosuppressive drugs such as cyclophosphamide can result in permanent ovarian failure [7]. In our study, a high proportion of women in their childbearing years with RDs were taking medications to treat their disease; NSAIDs were prescribed in 81.6% of patients, CSs in 77.8%, and DMARDs in 87.3%. This high prevalence of medication use in women with RDs in their childbearing years may contribute to the increased prevalence of comorbidities and also significantly affect childbearing by reducing reproductive potential. We found differences in the prevalence of comorbidities and medication use among the different RDs assessed. The prevalence of comorbidities was the highest in patients with SLE, followed by those with RA and AS. This may be related to increased odds for using CSs and DMARDs in patients with SLE and RA compared with those for patients with AS.

This study has several limitations. First, we only analyzed the prevalence of overall cancer, not specific types of prevalent cancer, as this study aimed to assess the burden of comorbidities on this particular population group from a broad perspective. Analysis of the prevalence of specific types of cancer in women of childbearing age with RDs might be the subject of another study. Second, the age- and sex-matched control subjects included patients taking DMARDs for other diseases, such as inflammatory bowel disease, seronegative RA, and non-radiographic spondyloarthropathy, although this proportion accounted for ≤ 0.6% of the control subjects. Despite these limitations, one strength is that this is the first study to use a nationwide database to estimate the burden of comorbidities and medication use in women of childbearing age with RDs.

In conclusion, Korean women with RDs have a heavy burden of comorbidities and medication use during their childbearing years compared with women without RDs of the same age. Therefore, special attention should be paid to this particular group of women with RDs in their childbearing years when allocating health resources and establishing policies related to comorbidities and medication use. Further research assessing the prevalence of other comorbidities associated with RDs including infection and osteoporosis may provide a more comprehensive understanding of the burden of comorbidities among women of childbearing age with RDs.
Conflict of interest
No potential conflict of interest relevant to this article was reported.

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