Effects of oral contraceptives on rheumatoid arthritis in Korean menopausal women: A nationwide cross-sectional study

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease with a multifactorial etiology. The higher prevalence of RA in women than in men may originate from differences in sex hormone levels or types. Ethnicity may interact with hormonal factors to produce various observed differences in the prevalence of RA. Oral contraceptives (OCs) are a source of exogenous sex hormones and can affect the prevalence of RA. We investigated the effects of OCs on RA in Korean menopausal women using a national data set. Data were collected from a cross-sectional study of 8789 eligible participants who completed the 2008–2012 Korea National Health and Nutrition Examination Survey. To balance the distribution of baseline characteristics between those participants who had ever used OCs and those who had not, we employed propensity score matching to adjust for differences. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for the effects of OCs on the incidence of RA. The development of RA in Korean women rapidly increased during the perimenopause. After propensity score matching, the use of OCs was associated with RA (OR 1.24, 95% CI 1.01–1.51, $P = 0.04$). However, hormone replacement therapy (HRT) was not associated with RA regardless of whether OCs had been used (OR 0.80, 95% CI 0.62–1.04, $P = 0.09$, and OR 1.00, 95% CI 0.66–1.52, $P = 0.99$, respectively). Our findings suggest that factors associated with sex hormones influence the prevalence of RA.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease. Various factors, including genetic and environmental factors, affect the development of RA [1]. Most autoimmune diseases have sex-related differences, and the prevalence of RA has a sex-related difference, with the prevalence in women being approximately twice that in men [2]. The predominance of RA in women may originate from hormonal factors, and hormonal factors influence pre-and post-menopausal women differently in RA development [3]. In addition, pregnancy and breast feeding can be protective against developing RA and the peak incidence of RA in women is during perimenopause [3–5]. It is suggested that estrogen and prolactin promote humoral immunity [6]. However, the difference in the incidence of RA due to the use of estrogen-containing oral contraceptives is not yet clear. The use of oral contraceptives (OCs) has been found to be protective against RA development in some studies but some meta-analyses were inconclusive [7,8]. Two mechanisms may explain the possible protection of OCs

against RA development. First, estrogen may reduce immune responses and modulate the secretion of pro-inflammatory cytokines [9]. Second, estrogen may inhibit formation of osteoclasts and a synovial pannus, thereby delaying the progression of RA [10].

RA is a heterogeneous disease that is affected by various factors, including genetic factors. Depending on the ethnicity, the disease course and treatment response differ [11]. Most previous studies on the association between RA and OC were performed mostly in Europe or North America, and the previous meta-analyses included only European and North American populations. Studies investigating the effect of OCs and menopause on RA are mainly based on non-Asian data. Studies in Asians were only conducted in China and showed that OC did not affect the development of RA [4]. The incidence and prevalence of RA significantly varies based on geography and some ethnic populations are at increased risk of RA. Environmental factors, genetic factors and their interaction may result in these differences. In addition, menopausal status was independently associated with an increased risk of RA [3,12]. Thus, we investigated the effect of the use of OCs on RA in

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Korean menopausal women using nationwide data.

2. Materials and methods

2.1. Study design and population

We conducted a nationwide cross-sectional study by using the Korea National Health and Nutrition Examination Survey (KNHANES), which collected data for four years between 2008 and 2012. Voluntary participants, who provided written informed consent, were included in the KNHANES. Households were randomly selected for participation, and sampled multi-stage stratification was based on geographical areas. The KNHANES was conducted in accordance with the Helsinki Declaration of 2000.

A total of 45,811 individuals participated in the 2008–2012 KHANES. Of these, 20,829 (45.5%) men and 7108 participants who did not complete the health survey sections regarding age, smoking, alcohol drinking, RA, menopause, OC, hypertension (HTN), or dyslipidemia were excluded. The menopausal status and cause of menopause (natural or surgical) were examined by the self-report of participants, and the subjects had natural menopause. Additionally, 9085 premenopausal women were excluded. The total number of eligible participants was 8789.

2.2. Main variables and covariates

The current diagnostic status of RA was based on self-reported data in response to the question "Are you diagnosed with or treated for RA by a physician?" RA was categorized as either "Yes" or "No". The use of OC was also based on self-reported data in response to the question "Have you ever used oral contraception?" Similarly, women were asked whether they were currently taking or had ever taken hormone replacement therapy (HRT). Menopause was defined at the health interview as no menstruation during the past 12 months. Data regarding age, smoking history, history of alcohol use, household income, menopausal status, and age at first delivery were collected during the health interview. During the physical examination, height, weight, and waist circumference were measured. Body mass index (BMI) was calculated as weight (kg) divided by height, squared (m^2).

Heavy alcohol consumption status was defined as consuming ≥5 units at least 2 days/week. The smoking group comprised current smokers and the non-smoking group comprised former smokers and those who had never smoked. For obesity classification, we classified the participants into three groups: 1) low weight group (BMI lower than 18.5 kg/m^2), 2) normal weight group (BMI between 18.5 and 25.0 kg/m^2), and 3) obese group (BMI higher than 25.0 kg/m^2), according to the Korea Centers for Disease Control and Prevention (KCDC) guidelines. Socioeconomic status was assessed based on monthly household income. Monthly household income was categorized into quartiles: lowest (USD < 918.3), medium-lowest (USD 918.3–1,836.5), medium-highest (USD 1,826.6–3,213.9), and highest (USD > 3213.9). HTN was defined as an average systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or use of antihypertensive medications. Diabetes mellitus (DM) was defined as a fasting plasma glucose (FPG) level ≥126 mg/dL, diagnosis of DM by a clinician, or use of an oral hypoglycemic agent or injected insulin. Dyslipidemia were defined as follows: total cholesterol ≥200 mg/dl, triglyceride ≥150 mg/dl, HDL-C < 50 mg/dl in women, or currently taking any anti-dyslipidemic drug for the purpose of controlling blood lipid concentrations.

2.3. Ethics statement

The institutional review board of the KCDC approved the study (IRB: 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012-01 EXP-01-2C). The informed consents provided to each participant when performing KNHANES is available from the

KCDC database (URL https://knhanes.cdc.go.kr/knhanes/sub04/sub04_01.do?classType=1). The requirement for informed consents for this study was exempted because it was a secondary analysis using the pre-existing KNHANES dataset.

2.4. Statistical analysis

According to the Korea Ministry of Health and Welfare and KCDC guidelines, we used the survey-weighted statistical analyses. Chi-square or Fisher's exact tests were used for categorical variables, t-tests for normal distribution, and Kruskal-Wallis tests for non-normal distribution of continuous variables to compare the demographic variables. We calculated the odds ratios (ORs) and 95% confidence intervals (CI) for RA according to OC use. We used a multivariable logistic regression model in which we adjusted for the confounding variables of age, alcohol intake, smoking status, BMI, household income, HTN, dyslipidemia, DM, menarche, menopause, menopause age, and age at first delivery. The SPSS ver. 23.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, and the IBM SPSS Statistics Version 23 − Essentials for R Version 23.0.0 (SPSS Inc., Chicago, IL, USA) was used for propensity score-matched analysis. A P value < 0.05 was considered significant.

2.5. Propensity score matching

To balance the distribution of baseline characteristics, we used propensity score matching. We estimated a propensity score for each study participant using the multivariable logistic regression model. In the model, potential confounders and variables associated with RA, such as age, alcohol intake, smoking status, BMI, household income, HTN, dyslipidemia, DM, and hormone replacement therapy (HRT) were included. We then created an exchangeable comparison group of patients using OCs by matching each with 2-fold patients not using OCs. Our propensity score model discriminated well between the OC and non-OC group. The model was fit to the data during all steps of the regression analyses (relative multivariate imbalance L1 after matching = 0.31). We then used the propensity score to match each patient using OCs (now or in the past) to 2 patients not using OCs who had a similar propensity score, thereby matching 1877 of patients using OCs to 3754 patients not using OCs. Our assessment of the covariate balance after matching focused on these standardized differences. After matching, the mean propensity score for the patients using OCs and not using OCs were 0.23 and 0.23, respectively.

3. Results

3.1. Prevalence of rheumatoid arthritis and baseline characteristics

Baseline patient characteristics between the OC and non-OC groups were significantly different (Table 1). In the group using OCs, patients were younger and more likely to be heavy drinkers, non-smokers, and to be in the lowest household income quartile. Prevalence of obesity, HTN, dyslipidemia, and DM were also higher than in the non-OC group. The weighted prevalence of RA in post-menopausal Korean was 5.9% which increased according to age (Table 2). Among those less than 55 years of age, the prevalence of RA was below 4.5%, but rapidly increased among those older than 55 years. The overall usage rate of OC was 20.6%, and the mean (± standard deviation [SD]) duration of OC use was 30.51 ± 38.75 months. The incidence of menopause for women in their 40 s was 42.5% and was 46.2% for those in their 50s. Median age of menopause was 49.0 years (25th quartile 46.0–75th quartile 52.0).

3.2. Effects of oral contraceptives on rheumatoid arthritis

After propensity score matching, baseline characteristics between