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Reproductive history and postmenopausal rheumatoid arthritis among women 60 years or older: Third National Health and Nutrition Examination Survey

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Abstract

Objective: Rheumatoid arthritis, a condition of unknown etiology, has been associated with considerable costs to society. The purpose of this study is to determine whether selected reproductive history characteristics are associated with postmenopausal rheumatoid arthritis diagnosis.

Methods: Secondary analyses were performed using cross-sectional data from the Third National Health and Nutrition Examination Survey. Of 1,892 eligible participants, 182 fulfilled the criteria for postmenopausal rheumatoid arthritis, based on self-report and the 1987 American College of Rheumatology criteria. Logistic regression models were constructed, and odds ratios (ORs) with their 95% CIs were calculated for selected reproductive history characteristics as predictors of postmenopausal rheumatoid arthritis, after adjustment for potential confounders.

Results: Multivariate logistic models suggested that age at menopause was the only reproductive characteristic that was significantly associated with the outcome of interest (OR, 0.96; 95% CI, 0.93-0.99). Compared with women experiencing menopause at 50 years of age or later, those who experienced menopause before 40 years of age (OR, 2.53; 95% CI, 1.41-4.53) had increased odds of postmenopausal rheumatoid arthritis.

Conclusions: Women who experience menopause before 40 years of age seem to be at increased risk for postmenopausal rheumatoid arthritis. Conversely, age at menarche and pregnancy history may not predict rheumatoid arthritis after menopause. Further research is needed to confirm and elucidate these epidemiological findings.

Key Words: Rheumatoid arthritis – Reproductive – Menopause – Survey.

Rheumatoid arthritis (RA), a long-term condition of unknown etiology, has been associated with considerable costs to society.[1-4] If not detected and managed early, RA can result in irreversible, painful, and disabling joint damage.[3] RA is often diagnosed using predefined criteria that necessitate clinical, laboratory, and radiologic examinations.[3] The prevalence of RA among adults is approximately 1%, affecting women two to four times more often than men.[1-3] Although RA risk increases with age, it can manifest at any stage of life, including childhood, adolescence, and adulthood. To date, a limited number of RA risk or protective factors have been identified, with genetic predisposition to autoimmune response (eg, *HLA-DR4* gene) and repeated environmental exposures (eg, tobacco smoke) playing a major role.[3] Heritability of RA is well-established because the lifetime risk of RA and related autoimmune diseases (namely, systemic lupus erythematosus, ankylosing spondylitis, scleroderma, Sjögren's syndrome, and hypothyroidism) increases 1.5 to 3 times in children of women diagnosed with RA.[5] Despite RA's inflammatory pathophysiology, no infectious agents have been clearly established as etiologic factors.[3] Thus, further research is needed to elucidate potential targets for RA prevention.

Sex differences in RA prevalence have long led to the suspicion that reproductive factors may alter RA risk in women.[6] Since 1958, women diagnosed with RA have been found to have fewer children compared with their healthy counterparts, although the underlying cause of this disparity ("infertility" or "personal choice") remains unclear.[5] Current evidence linking parity to RA risk remains inconclusive; some studies suggest that nulliparity is either protective against or a risk factor for RA, whereas other studies have failed to identify a significant relationship.[6] In addition, parity was found to reduce RA risk in case-control studies, but not in cohort studies.[5] Similarly, studies of breast-feeding, oral contraceptive use, age at menarche, age at first birth, age at menopause, and other reproductive characteristics have yielded inconsistent results.[1]

RA signs and symptoms may be ameliorated in the context of pregnancy and tend to flare up in postpartum, perimenopause, and early postmenopause,[1,2,6,7] implicating excessive

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or normal levels of female hormones (estrogen and progesterone) as protective factors against RA development.[1,7] To our knowledge, few studies have comprehensively analyzed reproductive history in relation to RA development in women,[1,2,5,7-18] and none of these studies have analyzed data from a nationally representative sample. The present study evaluates reproductive history and its association with RA diagnosed after menopause among women 60 years or older who participated in the Third National Health and Nutrition Examination Survey (NHANES III).

METHODS

Design and participants

A cross-sectional study was conducted using existing data sets from NHANES III. Since the 1960s, National Health and Nutrition Examination Surveys have been periodically conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. NHANES III (1988-1994), the seventh in a series of these surveys based on a complex multistage probability sample design, was designed to provide national estimates of the health and nutritional status of the 50 US states' civilian noninstitutionalized population 2 months or older. Details of the survey design and questionnaires are published elsewhere.[19] Briefly, a four-stage sample design was applied using primary sampling units (PSUs) composed mostly of single counties, followed by area segments within PSUs, households within area segments, and persons within households. Eighty-nine survey locations were randomly divided into two phases, with phase I consisting of 44 locations and with phase II consisting of 45 locations. PSUs of phase I were allocated to the first 3-year survey period (1988-1991), and PSUs of phase II were allocated to the second 3-year period (1991-1994). Accordingly, unbiased national estimates of health and nutrition characteristics can be independently produced for phase I, phase II, or total NHANES III, with the latter being the preferred option. Sources of data included interviews, physical examinations, and laboratory tests. The NHANES III protocol is compliant with the ethical rules for human experimentation stated in the Declaration of Helsinki, including the approval of an institutional review board and informed consent forms.

A total of 31,199 participants who had completed an adult interview, physical examinations, or laboratory testing were identified from phases I and II of NHANES III. Participants who satisfied the exclusion criteria—male sex (n = 15,900), younger than 60 years (n = 26,774), unknown arthritis status (n = 15,786), or nonmenopause status (n = 28,985)—were excluded from the study, leaving 1,892 eligible women.

Measures

Postmenopausal RA

The NHANES III database is composed of an "arthritis" component, namely, physician's examination of joints, certain serological tests, and self-reported data from the Adult Health Questionnaire, which was designed to identify individuals 60 years or older who are suffering from either RA or osteoarthritis. In this study, postmenopausal RA diagnosis ("yes" or "no") was defined using a modified version of the 1987 American College of Rheumatology (ACR) criteria,[20] along with self-reported RA history and age at menopause. In the absence of radiologic data, NHANES III participants who met three or more of six ACR criteria were identified as having RA, whereas those who met two or fewer ACR criteria were identified as not having RA.[21] ACR criteria included the following: presence of morning stiffness for at least 1 hour for at least 6 weeks; presence of arthritis in three or more joint areas; presence of arthritis in the joints of the hand; presence of symmetric arthritis; presence of rheumatoid nodules; and positive rheumatoid factor.[20,21] Among participants who met ACR criteria for RA, those who self-reported RA diagnosis by a health professional before menopause were not considered postmenopausal RA cases. Finally, participants who did not meet ACR criteria for RA but were diagnosed with RA after menopause were also considered postmenopausal RA cases.

Reproductive history

NHANES III comprises a "reproductive health" component, specifically the Mobile Examination Center Adult Questionnaire (women 17 y or older) or the home examination (women 20 y or older). For the current analyses, reproductive history was defined using the following indicators: age at menarche (continuous; <13, ≥13 y), age at menopause (continuous; <40, 40-49, ≥50 y), ever pregnant ("yes" or "no"), number of pregnancies (continuous; 0, 1-2, 3-5, ≥6), number of live births (continuous; 0, 1-2, 3-5, ≥6), age at first live birth (continuous; <20, 20-24, 25-29, 30-34, ≥35 y), age at last live birth (continuous; <20, 20-24, 25-29, 30-34, ≥35 y), hysterectomy ("yes" or "no") and oophorectomy ("yes" or "no"), oral contraceptives ("ever" or "never"), and hormone therapy ("ever" or "never").

Covariates

The hypothesized relationships between reproductive history and RA diagnosis were evaluated before and after adjustment for potential confounding factors, including age (continuous; <65, 65-69, 70-79, ≥80 y), education (less than high school, high school, more than high school), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), area of residence (metropolitan, other), poverty-to-income ratio (<100%, 100% to <200%, ≥200%), marital status (married/cohabiting, not married), and smoking status (current smoker, ex-smoker, never smoker). Sample size limitations and the complex survey design precluded the consideration of body mass index as a potential confounder for the hypothesized relationships.

Statistical analysis

Statistical analyses were performed using STATA version 12 (STATA Corp. College Station, TX). Whereas frequencies (%) were computed for categorical variables, means (SEM) were computed for continuous variables. Bivariate associations were examined using Pearson's χ^2 test. Crude odds ratios (ORs), adjusted ORs, and 95% CIs for hypothesized

relationships were calculated using the "svylogit" command. Several aspects of the National Health and Nutrition Examination Survey design were taken into account in data analysis, including sampling weights and the complex survey design. Three full-sample weights and four subsample weights are available in NHANES III. We applied the Mobile Examination Center examination weights on the current analyses. Sampling weights were used to produce correct population estimates of prevalence rates, means, and other statistics, accounting for differential probabilities of selection and adjusting for noncoverage, nonresponse, and oversampling of young children, older persons, black persons, and Mexican Americans. Furthermore, strata and PSU pairings were used to estimate variances and to test for statistical significance. Two-sided statistical tests were performed at an α level of 0.05.

RESULTS

The study sample consisted of 1,892 women with a mean age of 70.6 years (95% CI, 69.9-71.4). Nearly 28% had more than high school education, 86% were non-Hispanic white, 56% resided in nonmetropolitan areas, and 60% were at least 200% above the income-to-poverty ratio. Furthermore, 50% of these women were married or cohabiting, and 57% were never smokers. Two hundred fifty-eight women reported that they had been diagnosed with RA by a healthcare professional; of those, 76 were diagnosed before the onset of menopause, and the remaining 182 were diagnosed after menopause. Overall, the mean age at menopause and the mean age at self-reported RA diagnosis were 46.7 years (95% CI, 46.1-47.2) and 65.5 years (95% CI, 64.7-66.5), respectively. Although 36 women satisfied three or more of the 1987 ACR criteria for RA at the time of NHANES III, the case definition resulted in 182 postmenopausal RA women (Table 1).

TABLE 1. *Postmenopausal rheumatoid arthritis case definition (N = 1,892)*

Self-reported diagnosis	
No arthritis	1,289
Osteoarthritis	345
Rheumatoid arthritis	258
Before menopause	76
After menopause	182
1987 American College of Rheumatology criteria	
Criterion 1[a]	96
Criterion 2[b]	25
Criterion 3[c]	49
Criterion 4[d]	1,863
Criterion 5[e]	5
Criterion 6[f]	135
≤2 criteria	1,708
≥3 criteria	36
Postmenopausal rheumatoid arthritis	
Yes	182
No	1,710

[a]Morning stiffness for at least 1 hour for at least 6 weeks.
[b]Arthritis in three or more joint areas.
[c]Arthritis in the joints of the hand.
[d]Symmetric arthritis.
[e]Rheumatoid nodules.
[f]Positive rheumatoid factor.

Postmenopausal RA prevalence was estimated to be 7.9%, varying by selected sociodemographic and lifestyle characteristics. Specifically, women who had at least high school education seem to be protected against postmenopausal RA. Furthermore, non-Mexican blacks were two to three times more likely to be diagnosed with RA after menopause than non-Mexican whites. Although the prevalence of postmenopausal RA was negatively associated with a poverty-to-income ratio of at least 200% and with being married, these relationships were of borderline statistical significance. Differences in postmenopausal RA prevalence by age, area of residence, and smoking status were not statistically significant (Table 2).

Table 3 displays the bivariate and multivariate relationships of reproductive history characteristics with postmenopausal RA diagnosis. Bivariate analyses suggested that age at menarche and age at last live birth were not significantly associated with prevalent postmenopausal RA. By contrast, age at menopause and age at first live birth were inversely associated with postmenopausal RA, whereas number of pregnancies and number of live births were directly associated with postmenopausal RA. Furthermore, ever use of oral contraception or hormone therapy was not significantly related to postmenopausal RA. Finally, women who reported having undergone hysterectomy or oophorectomy did not have a significantly different postmenopausal RA prevalence compared with those who did not. Multivariate logistic models of reproductive history characteristics as predictors of postmenopausal RA were constructed. Age at menopause was the only reproductive characteristic associated with reduced odds of postmenopausal RA (OR, 0.96; 95% CI, 0.93-0.99) after controlling for age, education, race/ethnicity, area of residence, poverty-to-income ratio, marital status, and smoking status. Compared with women experiencing menopause at 50 years of age or later, those who experienced menopause before 40 years of age (OR, 2.53; 95% CI, 1.41-4.53) had increased odds of postmenopausal RA. Similar results were obtained after further adjustment for use of hormone therapy. The remaining reproductive history characteristics were not significantly associated with the outcome of interest after adjustment for confounders.

DISCUSSION

The present study evaluated whether selected reproductive history characteristics of older women could potentially be related to RA development after menopause. Using a nationally representative sample of NHANES III participants, we identified age at menopause among women 60 years or older to be the sole protective factor against postmenopausal RA, after adjustment for confounders. Specifically, the prevalence of postmenopausal RA was significantly higher among women whose age at menopause was less than 40 years compared with those who had their menopause at 50 years or later. We could not find a statistically significant relationship between postmenopausal RA and the remaining characteristics, namely, age at menarche, ever pregnant, number of pregnancies, number

TABLE 2. *Prevalence of postmenopausal rheumatoid arthritis by sociodemographic and lifestyle characteristics: Third National Health and Nutrition Examination Survey (N = 1,892)*

		Prevalence (%)[a]	Weighted COR (95% CI)	P^b
Age, mean (SEM), y	70.6 (0.4)		1.01 (0.9-1.04)	0.35
Age, n (%)				
<65 y	418 (26.1)	8.0	Ref	
65-69 y	386 (23.7)	5.8	0.71 (0.31-1.63)	0.41
70-74 y	398 (20.9)	8.8	1.11 (0.53-2.32)	0.79
75-79 y	273 (14.3)	8.8	1.13 (0.62-2.07)	0.68
≥80 y	417 (14.9)	8.8	1.11 (0.51-2.42)	0.79
Education, n (%)				
Less than high school	954 (35.9)	10.8	Ref	
High school	524 (36.4)	6.4	0.56 (0.34-0.92)	0.023
More than high school	414 (27.7)	6.1	0.54 (0.29-0.98)	0.043
Race/ethnicity, n (%)				
Non-Mexican white	1,198 (86.4)	7.2	Ref	
Non-Mexican black	297 (6.5)	15.6	2.37 (1.50-3.74)	<0.0001
Mexican American	326 (1.9)	10.4	1.48 (0.87-2.55)	0.15
Other	71 (5.2)	8.7	1.22 (0.49-3.06)	0.66
Area of residence, n (%)				
Metropolitan	801 (44.4)	7.9	Ref	
Other	1,091 (55.7)	7.9	1.01 (0.64-1.59)	0.97
Poverty-to-income ratio, n (%)				
<100	342 (11.2)	10.3	Ref	
100 to <200	555 (28.7)	10.6	1.03 (0.59-1.80)	0.92
≥200	771 (60.1)	6.3	0.59 (0.32-1.07)	0.082
Marital status, n (%)				
Married/cohabiting	819 (49.6)	6.5	Ref	
Not married	1,069 (50.4)	9.3	1.48 (0.96-2.27)	0.077
Smoking status, n (%)				
Current smoker	235 (14.7)	8.3	0.99 (0.42-2.33)	0.98
Ex-smoker	453 (28.5)	6.8	0.79 (0.46-1.36)	0.39
Never smoker	1,204 (56.9)	8.4	Ref	

COR, crude odds ratio; Ref, referent.
[a]Weighted means, standard errors, and proportions.
[b]*P* values for H_0 (COR = 1) versus H_A (COR ≠ 1).

of live births, age at first live birth, age at last live birth, hysterectomy status, oophorectomy status, and ever use of oral contraceptives or hormone therapy.

The results of this investigation should be interpreted with caution and in light of several limitations. First, we conducted secondary analyses using an existing data set, which limited our ability to devise items that would specifically address our research questions. Although the reproductive history questionnaire of NHANES III was sufficiently detailed to glean the information needed for the exposures of interest, we could not assess breast-feeding and irregular menstrual periods, which were previously found to be important determinants of RA.[1,8] Second, a cross-sectional design was adopted, precluding the establishment of cause-and-effect relationships. Third, the prevalence of RA was relatively low, thus reducing the power to detect the associations of various predictors, including cigarette smoking, with RA diagnosis. Fourth, unlike registry-based studies, RA case definition, more aptly named "inflammatory arthritis,"[22] was largely based on self-reported data that were not independently verified by healthcare professionals. Although rheumatoid factor can be positive at low titers, anticitrullinated protein antibodies would have enhanced the specificity of the case definition. Furthermore, NHANES III data limited our ability to clinically distinguish and exclude women with calcium pyrophosphate deposition, polymyalgia rheumatica, or gout. Finally, RA diagnosis could only be verified among women 60 years or older, reducing the generalizability of study findings.

Despite existing evidence for a sex differential in RA prevalence, a limited number of studies have tackled the putative association of reproductive factors with RA development.[1,2,8-11,15-17,23-27] Several biological mechanisms have also been proposed to explain why pregnancy may have a protective effect against future development of RA.[6] First, RA symptoms may be alleviated through microchimerism, whereby fetal DNA can circulate in maternal blood for decades after birth, resulting in broader self-recognition by the immune system. This beneficial effect of microchimerism is expected to wane with time since last pregnancy.[6] Second, maternal-fetal disparity in human leukocyte antigen class II antigens may be important for reducing RA symptoms during pregnancy.[6] Third, pregnancy can delay the onset of RA symptoms with better prognosis. In fact, pregnancy is accompanied by complex variations in hormone levels, cytokine profiles, and immune cell function.[7] Estrogen, progesterone, and cortisol levels increase during the course of a pregnancy, favoring cytokine profiles and $CD4^+$ regulatory T-cells that counter cell-mediated autoimmunity, all of which substantially decline in the postpartum period.[7] Fourth, nulliparous women may be at increased risk for inflammation of multiple joints, potentially because of hormonal imbalances resulting from infertility, a heterogeneous condition affecting 10% of

TABLE 3. *Prevalence of postmenopausal rheumatoid arthritis by reproductive history characteristics: Third National Health and Nutrition Examination Survey (N = 1,892)*

		Prevalence (%)[a]	Weighted COR (95% CI)	P^b	Weighted AOR (95% CI)[c]
Age at menarche, mean (SEM), y	13.0 (0.06)		1.01 (0.89-1.15)	0.87	0.99 (0.86-1.14)
Age at menarche, n (%)					
<13 y	602 (39.7)	7.4	Ref		Ref
≥13 y	1,060 (60.3)	7.5	1.03 (0.68-1.55)	0.90	0.91 (0.57-1.47)
Age at menopause, mean (SEM), y	46.7 (0.3)		0.96 (0.93-0.98)	0.003	0.96 (0.93-0.99)
Age at menopause, n (%)					
<40 y	289 (14.7)	14.7	2.53 (1.49-4.30)	0.001	2.53 (1.41-4.53)
40-49 y	831 (43.6)	7.1	1.13 (0.39-1.83)	0.62	1.11 (0.69-1.77)
≥50 y	772 (41.6)	6.4	Ref		Ref
Ever pregnant, n (%)					
Yes	1,533 (88.5)	8.0	Ref		Ref
No	210 (11.5)	7.2	0.89 (0.48-1.69)	0.73	0.79 (0.38-1.70)
Number of pregnancies, mean (SEM)	3.3 (0.1)		1.06 (1.00-1.13)	0.04	1.05 (0.98-1.13)
Number of pregnancies, n (%)					
0	210 (11.5)	7.2	Ref		Ref
1-2	501 (31.7)	7.5	1.04 (0.51-2.13)	0.91	1.21 (0.52-2.84)
3-5	645 (41.6)	6.9	0.96 (0.47-1.95)	0.90	1.15 (0.51-2.62)
≥6	386 (15.3)	11.9	1.73 (0.86-3.46)	0.12	1.68 (0.75-3.74)
Number of live births, mean (SEM)	2.7 (0.07)		1.09 (1.01-1.17)	0.024	1.07 (0.98-1.16)
Number of live births, n (%)					
0	269 (14.5)	7.9	Ref		Ref
1-2	601 (39.4)	6.7	0.84 (0.45-1.54)	0.56	0.97 (0.48-1.96)
3-5	584 (36.0)	7.8	0.99 (0.51-1.89)	0.97	1.10 (0.53-2.29)
≥6	288 (10.1)	13.4	1.81 (0.97-3.36)	0.061	1.68 (0.83-3.39)
Age at first live birth, mean (SEM), y	23.5 (0.2)		0.95 (0.89-0.99)	0.027	0.96 (0.90-1.02)
Age at first live birth, n (%)					
<20 y	836 (32.4)	8.6	Ref		Ref
20-24 y	585 (37.9)	9.9	1.17 (0.73-1.90)	0.50	1.47 (0.89-2.41)
25-29 y	304 (21.4)	5.0	0.57 (0.25-1.29)	0.17	0.83 (0.32-2.12)
30-34 y	102 (5.4)	4.0	0.45 (0.12-1.61)	0.21	0.41 (0.09-1.88)
≥35 y	53 (2.8)	6.9	0.79 (0.23-2.68)	0.69	0.99 (0.30-3.29)
Age at last live birth, mean (SEM), y	30.9 (0.2)		0.99 (0.95-1.03)	0.64	0.98 (0.94-1.02)
Age at last live birth					
<20 y	489 (18.1)	9.3	Ref		Ref
20-24 y	196 (12.9)	10.1	1.09 (0.54-2.24)	0.79	1.21 (0.52-2.79)
25-29 y	290 (21.2)	5.6	0.58 (0.26-1.33)	0.19	0.65 (0.28-1.53)
30-34 y	307 (20.3)	8.2	0.88 (0.44-1.74)	0.70	1.13 (0.52-2.46)
≥35 y	532 (27.6)	6.9	0.73 (0.37-1.45)	0.36	0.76 (0.38-1.53)
Hysterectomy, n (%)					
Yes	695 (38.5)	9.4	Ref		Ref
No	1,173 (61.5)	6.8	0.69 (0.44-1.11)	0.13	0.65 (0.39-1.10)
Oophorectomy, n (%)					
Yes	468 (27.6)	9.2	Ref		Ref
No	1,334 (72.5)	7.4	0.77 (0.48-1.29)	0.34	0.79 (0.48-1.32)
Oral contraceptives, n (%)					
Yes	175 (9.3)	6.1	0.73 (0.31-1.72)	0.46	0.83 (0.29-2.42)
No	1,714 (90.7)	8.1	Ref		Ref
Hormone therapy, n (%)					
Yes	584 (33.8)	8.3	1.14 (0.74-1.76)		1.46 (0.85-2.49)
No	1,142 (66.2)	7.3	Ref		Ref

COR, crude odds ratio; AOR, adjusted odds ratio; Ref, referent.
[a]Weighted means, standard errors, and proportions.
[b]*P* values for H_0 (COR = 1) versus H_A (COR ≠ 1).
[c]Each model corresponding to one reproductive history characteristic was adjusted for a priori confounding variables, including age (years), education, race/ethnicity, area of residence, poverty-to-income ratio, marital status, and smoking status.

the general population and 25% of women diagnosed with RA.[5,6] T_H1/T_H2 imbalance, with T_H1 predominance over T_H2, can potentially explain the excessive inflammation observed in RA-diagnosed women, as well as the beneficial effects of preexisting atopy and pregnancy on RA signs and symptoms.[18] Whereas a low T_H1/T_H2 ratio promotes successful pregnancy, a high T_H1/T_H2 ratio (a characteristic of RA-diagnosed women) has the potential to reduce fertility and fecundity and to increase the likelihood of spontaneous abortion.[18]

Parity has been the most widely examined reproductive characteristic in relation to RA development. The weight of evidence in recent studies seems to be divided between negative[7,11] and null associations.[8,10] For instance, in a case-control study involving high-risk North American Natives, Peschken et al[7] compared RA-affected women (n = 168) with their nonaffected relatives (n = 400) on reproductive history and found that women who had six or more births had a reduced likelihood of developing RA compared with women who had one to two births (OR, 0.43; 95% CI, 0.21-0.87).

Similarly, Jorgensen et al[11] conducted a large cohort study of 4.4 million people from the Danish National Register to evaluate the effects of live birth, pregnancy loss, and complication on the subsequent risk of RA hospitalizations in both men (n = 3,041) and women (n = 7,071). Poisson regression analyses suggested that nulliparity was not associated with RA risk; however, compared with women with one child, those who had two (relative risk, 0.84; 95% CI, 0.78-0.90) or three (relative risk, 0.83; 95% CI, 0.77-0.91) children were at lower risk for RA. Although breast-feeding was a key protective factor, parity was not related to mention of RA in death certificates in a cohort study of 63,090 women followed up from 1961 to 1989.[8] By the same token, a cohort study of 121,700 female nurses aged 30 to 55 years found no significant relationship between parity and RA risk.[10]

Reproductive characteristics besides parity were scarcely evaluated, and these include age at menarche,[1,8,10] age at first live birth,[1,2] age at last live birth,[1,2] and age at menopause,[2,8,10,17] as well as breast-feeding,[1,8] irregular menstrual periods,[1] pregnancy complications, and loss.[11] The current study revealed that age at menopause was the only significant risk factor for RA development in the postmenopausal period among women 60 years or older. Previous studies found nonsignificant[8,10] or inverse[2,17] relationships between later age at menopause and RA development in a more heterogeneous population. Recently, Pikwer et al[13] conducted a nested case-control study based on 18,326 women who participated in a community-based health survey between 1991 and 1996 involving self-administered questionnaires, linkage to Swedish RA registers (using 1987 ACR criteria), and 1:4 case-to-control matching. Consistent with our study findings, early age at menopause (≤45 y) was associated with subsequent development of RA (OR, 1.92; 95% CI, 1.02-3.64) after adjusting for key confounders.

CONCLUSIONS

Women who experience menopause at 40 years of age or earlier seem to be at risk for postmenopausal RA. Thus, the group at high risk for RA development after menopause consists of women who reach menopause prematurely, including women with premature ovarian failure. This finding is consistent with some, but not all, previous investigations. By contrast, age at menarche and pregnancy history do not predict RA after menopause. Further research is needed to confirm and elucidate epidemiological findings.

REFERENCES

1. Karlson EW, Mandl LA, Hankinson SE, Grodstein F. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study. *Arthritis Rheum* 2004; 50:3458-3467.
2. Merlino LA, Cerhan JR, Criswell LA, Mikuls TR, Saag KG. Estrogen and other female reproductive risk factors are not strongly associated with the development of rheumatoid arthritis in elderly women. *Semin Arthritis Rheum* 2003;33:72-82.
3. Ngian GS. Rheumatoid arthritis. *Aust Fam Physician* 2010;39:626-628.
4. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. *J Autoimmun* 2009;33:197-207.
5. Clowse ME, Chakravarty E, Costenbader KH, Chambers C, Michaud K. Effects of infertility, pregnancy loss, and patient concerns on family size of women with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2012;64:668-674.
6. Camacho EM, Harrison M, Farragher TM, et al. Parity, time since last live birth and long-term functional outcome: a study of women participating in the Norfolk Arthritis Register. *Ann Rheum Dis* 2011;70:642-645.
7. Peschken CA, Robinson DB, Hitchon CA, et al. Pregnancy and the risk of rheumatoid arthritis in a highly predisposed North American Native population. *J Rheumatol* 2012;39:2253-2260.
8. Brun JG, Nilssen S, Kvale G. Breast feeding, other reproductive factors and rheumatoid arthritis. A prospective study. *Br J Rheumatol* 1995; 34:542-546.
9. Del Junco DJ, Annegers JF, Coulam CB, Luthra HS. The relationship between rheumatoid arthritis and reproductive function. *Br J Rheumatol* 1989;28(suppl 1):33, discussion 35-42.
10. Hernandez Avila M, Liang MH, Willett WC, et al. Reproductive factors, smoking, and the risk for rheumatoid arthritis. *Epidemiology* 1990; 1:285-291.
11. Jorgensen KT, Pedersen BV, Jacobsen S, Biggar RJ, Frisch M. National cohort study of reproductive risk factors for rheumatoid arthritis in Denmark: a role for hyperemesis, gestational hypertension and preeclampsia? *Ann Rheum Dis* 2010;69:358-363.
12. McHugh NJ. Pregnancy loss, menopause, and the onset of rheumatoid arthritis. *Ann Rheum Dis* 1990;49:817-818.
13. Pikwer M, Bergstrom U, Nilsson JA, Jacobsson L, Turesson C. Early menopause is an independent predictor of rheumatoid arthritis. *Ann Rheum Dis* 2012;71:378-381.
14. Pikwer M, Nilsson JA, Bergstrom U, Jacobsson LT, Turesson C. Early menopause and severity of rheumatoid arthritis in women older than 45 years. *Arthritis Res Ther* 2012;14:R190.
15. Silman AJ. Reproductive events and the risk of development of rheumatoid arthritis. *Scand J Rheumatol Suppl* 1998;107:113-115.
16. Silman AJ, Roman E, Beral V, Brown A. Adverse reproductive outcomes in women who subsequently develop rheumatoid arthritis. *Ann Rheum Dis* 1988;47:979-981.
17. Skare TL, Mendes LR. [Influence of reproductive factors in the clinical and laboratory parameters of rheumatoid arthritis]. *Rev Bras Ginecol Obstet* 2011;33:132-136.
18. van Dunne FM, Lard LR, Rook D, Helmerhorst FM, Huizinga TW. Miscarriage but not fecundity is associated with progression of joint destruction in rheumatoid arthritis. *Ann Rheum Dis* 2004;63:956-960.
19. National Center for Health Statistics. *Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988-94*. Washington, DC: US Department of Health & Human Services, Public Health Service, Centers for Disease Control & Prevention, National Center for Health Statistics, 1994.
20. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-324.
21. de Pablo P, Dietrich T, McAlindon TE. Association of periodontal disease and tooth loss with rheumatoid arthritis in the US population. *J Rheumatol* 2008;35:70-76.
22. Lahiri M, Luben RN, Morgan C, et al. Using lifestyle factors to identify individuals at higher risk of inflammatory polyarthritis (results from the European Prospective Investigation of Cancer-Norfolk and the Norfolk Arthritis Register—the EPIC-2-NOAR Study) [epub ahead of print]. *Ann Rheum Dis* 2013.
23. Brennan P, Ollier B, Worthington J, Hajeer A, Silman A. Are both genetic and reproductive associations with rheumatoid arthritis linked to prolactin? *Lancet* 1996;348:106-109.
24. da Silva JA. Heat shock proteins: the missing link between hormonal and reproductive factors and rheumatoid arthritis? *Ann Rheum Dis* 1991;50: 735-739.
25. Lazowski Z, Janczewski Z, Polowiec Z. The effect of alkylating agents on the reproductive and hormonal testicular function in patients with rheumatoid arthritis. *Scand J Rheumatol* 1982;11:49-54.
26. Martinez Lopez JA, Loza E, Carmona L. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). *Clin Exp Rheumatol* 2009;27: 678-684.
27. Reckner Olsson A, Skogh T, Wingren G. Comorbidity and lifestyle, reproductive factors, and environmental exposures associated with rheumatoid arthritis. *Ann Rheum Dis* 2001;60:934-939.