Pregnancy and the Risk of Rheumatoid Arthritis in a Highly Predisposed North American Native Population

CHRISTINE A. PESCHKEN, DAVID B. ROBINSON, CAROL A. HITCHON, IRENE SMOLIK, DONNA HART, CHARLES N. BERNSTEIN, and HANI S. EL-GABALAWY

ABSTRACT. ***Objective.*** To examine reproductive history and rheumatoid arthritis (RA) risk in a highly predisposed population of North American Natives (NAN) with unique fertility characteristics.

Methods. The effect of pregnancy on the risk of RA was examined by comparing women enrolled in 2 studies: a study of RA in NAN patients and their unaffected relatives; and NAN patients with RA and unrelated healthy NAN controls enrolled in a study of autoimmunity. All participants completed questionnaires detailing their reproductive history.

Results. Patients with RA (n = 168) and controls (n = 400) were similar overall in age, education, shared epitope frequency, number of pregnancies, age at first pregnancy, smoking, and breastfeeding history. In multivariate analysis, for women who had ≥ 6 births the OR for developing RA was 0.43 (95% CI 0.21-0.87) compared with women who had 1-2 births (p = 0.046); for women who gave birth for the first time after age 20 the OR for developing RA was 0.33 (95% CI 0.16-0.66) compared with women whose first birth occurred at age ≤ 17 (p = 0.001). The highest risk of developing RA was in the first postpartum year (OR 3.8; 95% CI 1.45-9.93) compared with subsequent years (p = 0.004).

Conclusion. In this unique population, greater parity significantly reduced the odds of RA; an early age at first birth increased the odds, and the postpartum period was confirmed as high risk for RA onset. The protective effect of repeated exposure to the ameliorating hormonal and immunological changes of pregnancy may counterbalance the effect of early exposure to the postpartum reversal of these changes. (First Release Oct 15 2012; J Rheumatol 2012;39:2253–60; doi:10.3899/jrheum.120269)

Key Indexing Terms:
PREGNANCY RHEUMATOID ARTHRITIS RISK FACTORS
ETHNIC GROUPS NORTH AMERICAN NATIVES

The amelioration of rheumatoid arthritis (RA) symptoms during pregnancy and the tendency for symptoms to flare in the postpartum period have led to the suspicion that pregnancy and childbirth may influence the risk of developing RA. However, previous studies that have evaluated the correlation between RA risk and pregnancy history have shown conflicting results. Parity was found to reduce the risk of RA in a case-control study by Spector, *et al*, comparing women with RA to women with osteoarthritis (OA) and randomly selected controls[1]. Another case-control study, comparing 135 patients with RA to 378 controls with OA or soft tissue disorders also found a reduced risk of RA of 0.49 (95% CI 0.27–0.91) for parous women compared with nulliparous women[2]. However, a large Finnish study of > 15,000 women, using a population register, did not find any association between parity and subsequent risk of developing RA[3]. Similarly, Karlson, *et al* studied female reproductive and hormonal risk factors for RA in 121,700 women enrolled in the Nurses' Health Study, and did not find an association between parity and increased risk of RA in this cohort[4].

North American Natives (NAN) from several tribal groups, including those from Central Canada[5], have been found to have among the highest prevalence rates of RA in the world[6], with a young age at onset[6,7]. We have previously shown that the NAN population from central Canada has a prevalence of RA of 2–3%[5] as well as a high background frequency of the shared epitope alleles, with 75% of the entire population having at least 1 copy[8]. In addition to

From the Arthritis Centre, Section of Rheumatology, and the Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.

Dr. El-Gabalawy received financial support from Canadian Institutes of Health Research (CIHR) grant MOP7770. Dr. Bernstein received financial support from CIHR grant IIN 84040.

C.A. Peschken, MD, MSc, FRCPC, Assistant Professor, Departments of Medicine and Community Health Sciences; D.B. Robinson, MD, MSc, FRCPC, Associate Professor; C.A. Hitchon, MD, MSc FRCPC, Associate Professor; I. Smolik, PhD, Research Associate; D. Hart, RN, BN, Research Nurse; C.N. Bernstein, MD, FRCPC, Professor of Medicine; H.S. El-Gabalawy, MD, FRCPC, Department of Medicine, University of Manitoba.

Address correspondence to Dr. C.A. Peschken, Arthritis Centre, University of Manitoba, RR149, 800 Sherbrook St., Winnipeg, Manitoba R3A 1M4, Canada. E-mail: cpeschken@hsc.mb.ca

Accepted for publication August 20, 2012.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org

prevalent genetic risk factors, cigarette smoking, the most consistently documented environmental risk factor for RA, is also very prevalent in this population at 59%, nearly 3 times the rate of the general Canadian population[9,10]. Fertility statistics differ significantly between NAN women and the general Canadian population: The birth rate for Canadian women has been relatively low for several decades, and was reported at 1.5 births/woman in 2002. Although the birth rate has declined sharply for NAN women, it remains almost twice as high at 2.9/woman in 2000[11]. Age at first birth also differs: 22% of all births to NAN women occurred between the ages of 15 and 19 years, compared with 5.6% of all babies born in Canada in 1997 to mothers in this age group. Similarly, in the 20- to 24-year-old age group, the proportions were 32.3% and 18.2%, respectively[11]. We therefore decided to explore the relationship between parity and childbirth and the risk of RA in this highly predisposed population with unique fertility characteristics. We analyzed pregnancy history and RA risk using detailed data from NAN participants in 2 separate studies: the first is a study of risk factors for development of RA, comparing patients with RA and their unaffected relatives; the second is a study of autoimmunity in NAN, comparing RA and inflammatory bowel disease (IBD).

MATERIALS AND METHODS

Female participants in 2 separate studies were included in this analysis.

Study 1 was Early Detection of Rheumatoid Arthritis in First Nations (Canadian Institutes of Health Research MOP7770). Patients with RA were recruited from a Cree and Ojibway NAN population in central Canada. Patients visiting rheumatology clinics in urban (Winnipeg, Saskatoon) and rural (Norway House, St. Theresa's Point) locations were enrolled and approached to bring along unaffected relatives who were willing to participate. All study subjects were over 18 years of age. The unaffected population consisted mainly of first-degree relatives (76%) and was composed of siblings and offspring, with the remainder being second-degree relatives (cousins, nieces, nephews).

Study 2 was the Arthritis and Inflammatory Bowel Disease (AIBD) in First Nations (Canadian Institutes of Health Research IIN 84040). NAN patients with RA and healthy unrelated NAN controls without a personal or family history of chronic immune diseases were enrolled in a cohort study aimed to determine differences between First Nations and whites with IBD or RA. The AIBD study also included a white comparison group, but only the NAN patients with RA and controls were included for analysis in our study. The patients with RA were enrolled from patients attending rheumatology clinics in Winnipeg, and the healthy controls were enrolled through community advertisements. All participants in both studies were required to have at least 3 of 4 grandparents of First Nations ethnicity (99% had 4 NAN grandparents).

All participants in both studies completed identical questionnaires detailing reproductive history, including questions on age at first pregnancy, dates of each pregnancy, outcome of each pregnancy, and breastfeeding history. Questions on hormonal contraception were also included. All patients met the American College of Rheumatology classification criteria for RA[12] and the diagnosis was confirmed by a rheumatologist. Patients with RA onset before menarche were excluded from analyses. All controls filled out a questionnaire and were examined by a rheumatologist to check for the absence of inflammatory arthritis or other autoimmune disease. Questionnaires also included educational attainment and detailed smoking history. Smokers for this analysis were defined as current smokers versus nonsmokers. All participants gave written consent, and the Biomedical Research Ethics Boards of the University of Manitoba and the Band Councils of each rural community approved both protocols. Research Ethics Board no. H2005:093.

Determination of risk period for RA for cases and controls. In most previous studies examining reproductive factors and the risk of RA, investigators have enrolled patients with RA who were at or near the onset of their disease, and have chosen age-matched controls using a variety of methods[13,14,15,16,17]. Our patients with RA already had established disease, and on average were about 10 years older than the controls. We therefore used the date of study enrollment as the assigned "dummy date of RA onset" for controls, to compare to the date of RA onset for patients. This then resulted in similar age at RA onset and age at study enrollment for cases and controls (Table 1).

Risk factors evaluated. Risk factors evaluated included age at menarche, age at first birth, total number of pregnancies (parity), and the time elapsed between the last pregnancy and the onset of RA. For patients with RA, only pregnancies occurring before the onset of RA were included in the analyses, and for all participants, only pregnancies ending in live births or stillbirths were included. Oral contraceptive use and breastfeeding history were also evaluated, and the number of copies of the shared epitope was evaluated, along with age, educational attainment, and smoking status.

HLA genotyping of RA cases and controls. DNA was extracted from whole blood, and HLA-DRB1 typing was performed as described[8].

Statistical analysis. As there were no differences between the RA cases from the 2 studies and the related and unrelated controls with respect to age, smoking status, education, or parity characteristics (data not shown), only 2-group comparisons (RA cases vs controls) were performed. Age, age at first birth, and parity were categorized according to the distribution of the variables for the entire cohort. Age at menarche was compared using the t-test for comparison of means. The distribution of shared epitope alleles according to the number of copies was compared across parity status between RA cases and controls using the chi-square test for trend. Similarly, nulliparity, oral contraceptive use (ever or never), number of births, age at first birth, and time elapsed since last pregnancy were compared between cases and controls using the chi-squared test for trend. In analyzing the breastfeeding data, it was found that almost 70% of both cases and controls had breastfed either not at all or for < 3 months (data not shown); therefore this variable was not included in subsequent analyses. Because the proportion of cases (at the onset of RA) and controls who were nulliparous was small, we chose to focus on parous women for the multivariate analysis of associations between parity characteristics and the risk of RA. Logistic regression models were used to estimate the association between disease status and number of children, age at the time of first birth, and time that had elapsed since the last birth, with adjustment for age, education, and smoking status. Analyses were performed using SPSS software, version 18 (IBM).

RESULTS

A total of 168 NAN patients with RA and 400 NAN controls were included in our study. One hundred forty-one patients with RA and 197 of their relatives (control group 1) were participants in Study 1 of risk factors for RA. Twenty-seven NAN patients with RA were participants in Study 2, along with 203 unrelated healthy NAN controls (control group 2). There were no differences between control groups 1 and 2 with respect to age, smoking status, education, or parity characteristics, and thus the 2 groups were combined. The baseline characteristics of the patients and controls are presented in Table 1. After adjustment of the age of patients with RA to age at RA onset, there were no differences in age

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org

Table 1. Baseline characteristics of North American Native patients with rheumatoid arthritis (RA) and controls.

Study Participants	Patients with RA	Controls	Totals	p
Early Detection of RA study	141	197	338	
Arthritis and IBD in First Nations study	27	203	230	
Total	168	400	568	
RA disease duration, mean ± SD, yrs	12 ± 9.3			
Age at RA onset, mean ± SD, yrs	37 ± 12			
RF positive (%)	149/168 (89)			
Receiving DMARD (%)	156/168 (93)			
Age at study baseline, mean ± SD, yrs	46 ± 12	36 ± 12		< 0.001
Age adjusted to age at RA onset, mean ± SD, yrs	37 ± 12	36 ± 12		NS
Age category, yrs, % (n)*				
15–24	16 (27)	22 (88)		NS
25–34	26 (44)	29 (115)		—
35–44	27 (46)	25 (101)		—
> 45	30 (51)	24 (96)		—
High school completion, % (n)	37 (62)	35 (140)		NS
Smoker, % (n)	81 (136)	77 (308)		NS

* Age adjusted to age at RA onset for patients with RA. IBD: inflammatory bowel disease; RF: rheumatoid factor; DMARD: disease-modifying antirheumatic drug.

between cases and controls (37 ± 12 yrs vs 36 ± 12 yrs, p = ns). Educational level attained, measured as high school completion, was similarly low in both groups (37% for cases vs 35% for controls; p = ns), and smoking rates were similarly high (81% for cases vs 75% for controls; p = ns).

Shared epitope. There were no differences in the proportion of RA cases and controls having 0, 1, or 2 copies of the shared epitope: 25% of all study participants had 2 copies of the shared epitope, 48% had 1 copy, and 27% had none. There were also no associations between parity and number of shared epitope copies (data not shown).

Reproductive characteristics. The mean age at menarche was slightly younger in RA cases compared to controls, at 12.7 years versus 13.3 years; p = 0.002 (Table 2). Our data on oral contraceptive use overall, and in particular with reference to the onset of RA for cases, were incomplete. As there were no differences between cases and controls in "ever" use of oral contraceptives, this variable was not

Table 2. Reproductive characteristics of North American Native patients with rheumatoid arthritis (RA) and controls.

Characteristics	Cases, n = 168	Controls, n = 400	p
Age at menarche, yrs ± SD	13.3 ± 1.6	12.7 ± 1.5	< 0.002
Nulliparous*, % (n)	12 (20)	14 (56)	NS
Oral contraceptive use (ever)	51% (71)	38% (131)	NS
Characteristics of parous women	Cases (148)	Controls (344)	
Age at first birth, yrs, % (n)			0.060
< 17	34 (51)	35 (120)	
17–18	22 (33)	13 (45)	
19–20	22 (33)	25 (87)	
> 20	21 (31)	27 (92)	
* No. pregnancies, % (n)			0.773
1–2	32 (47)	29 (99)	
3	14 (21)	17 (58)	
4–5	29 (43)	31 (105)	
≥ 6	25 (37)	24 (82)	
Time elapsed since last pregnancy**, yrs, % (n)			< 0.002
< 1	15 (22)	7 (24)	
1–5	17 (25)	34 (117)	
6–15	20 (30)	16 (54)	
> 15	48 (71)	43 (149)	

* Parity adjusted to parity at onset of RA for cases. ** Calculated as the time elapsed between the last pregnancy and RA onset for RA cases and time elapsed between the last pregnancy and study enrollment for controls.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org

included in multivariate analyses. Only a small proportion of cases (at the onset of RA) at 12% and controls at 14% were nulliparous; therefore we chose to focus on parous women, and examined associations between age at first birth, the number of pregnancies, the timing from last pregnancy to RA onset, and the risk of RA.

There was a trend for a younger age at first birth in cases compared to controls, with 56% of cases giving birth at or before age 18 compared to 48% of controls ($p = 0.06$). There were no differences in the proportion of cases or controls having 1–2 pregnancies (32% vs 29%); 3 pregnancies (14% vs 17%); 4–5 pregnancies (29% vs 31%); or 6 or more pregnancies (25% vs 24%).

Figure 1 shows the distribution of years from last pregnancy to the onset of RA, and illustrates the increased frequency of RA onset in the first year compared to later years. When compared to the control group, there were significant differences in time elapsed since last pregnancy. This was calculated as the time elapsed between the last pregnancy before onset of RA for RA cases and time elapsed between the last pregnancy and study enrollment (dummy RA onset variable) for controls. Fifteen percent of cases developed RA within 1 year of a pregnancy, compared to 7% of controls; for 17% of cases and 34% of controls, 1–5 years elapsed between last pregnancy and RA onset or study enrollment; 5–15 years elapsed for 20% and 16% of cases and controls respectively, and for 48% of cases and 43% of controls, more than 15 years elapsed between last pregnancy and RA onset or study enrollment; $p < 0.002$ (Table 2).

In multivariate logistic regression analysis (Figure 2), only those women who had had at least 1 full term pregnancy before RA onset for cases (n = 148) or study enrollment for controls (n = 344) were included. Age, smoking status, education, age at menarche, age at first birth, number of births, and time elapsed since last pregnancy were included in the analysis. A later age at menarche slightly increased the OR of developing RA (ß 0.270, OR 1.3; 95% CI 1.1–1.5). Women who had 6 or more births had an OR of less than half for developing RA compared with women who had 1–2 births (OR 0.43; 95%

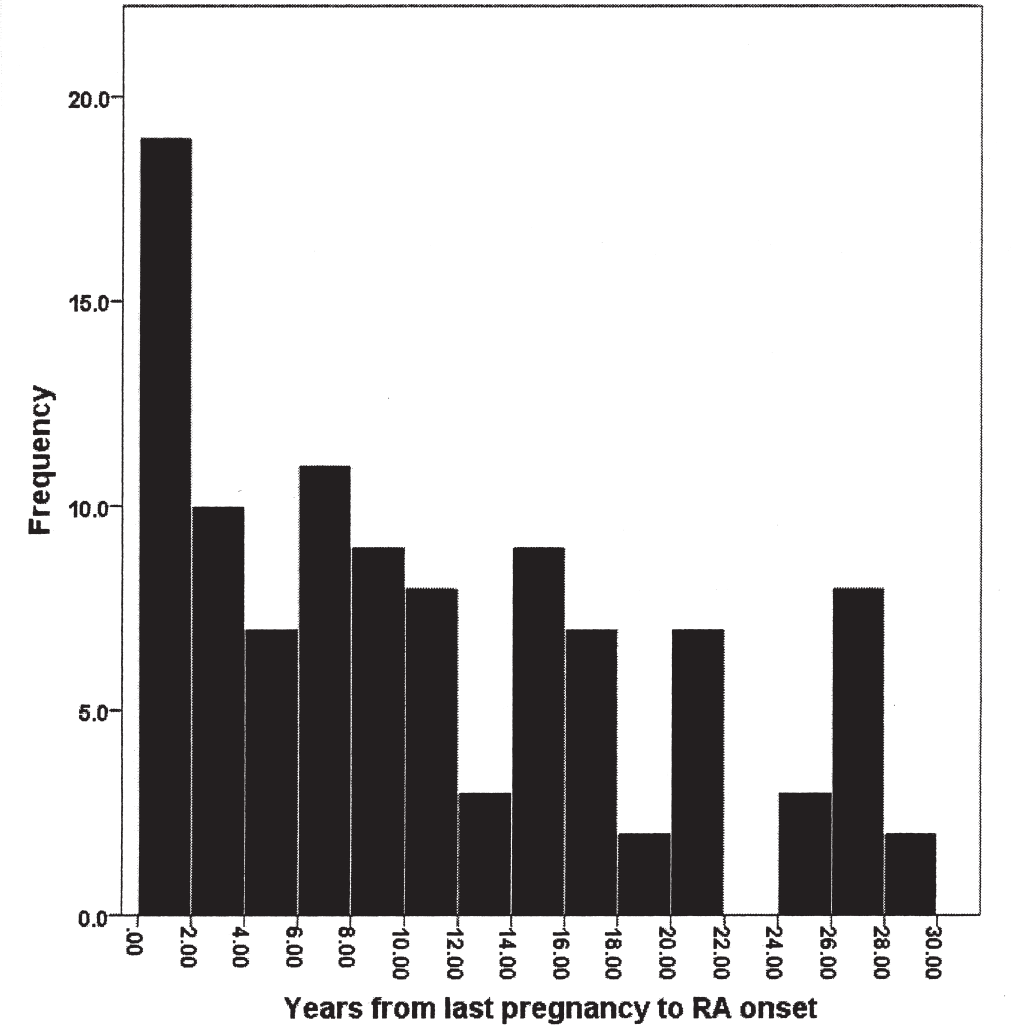

Figure 1. For patients with rheumatoid arthritis (RA), years from last pregnancy to onset of RA.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org

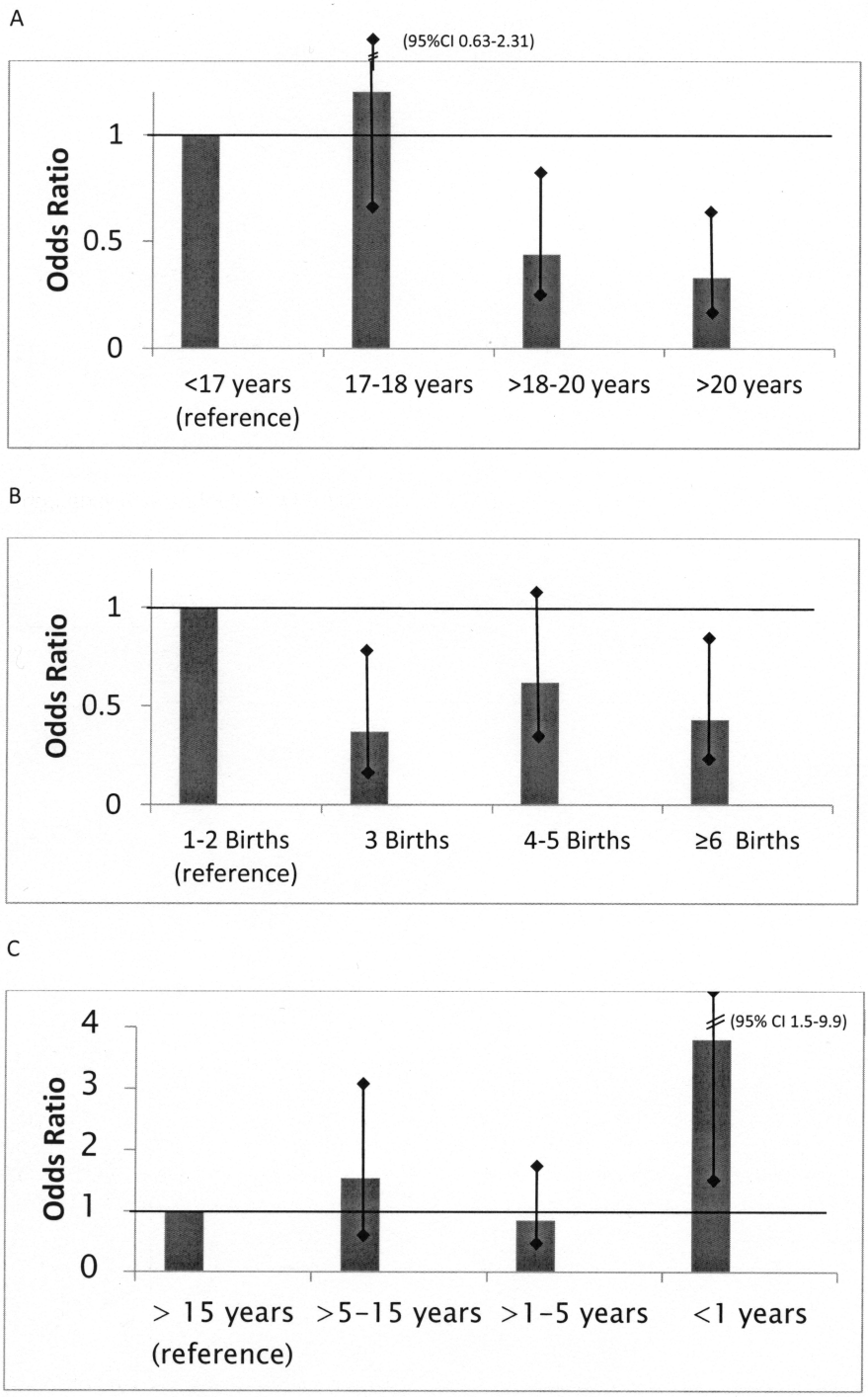

Figure 2. Adjusted OR for developing rheumatoid arthritis by parity characteristics in parous women. OR adjusted for age, smoking status, education, and age at menarche. A. Age at first birth. B. Number of births. C. Time elapsed since last birth.

CI 0.21–0.87, overall p for trend 0.046; Figure 2A). Women who gave birth for the first time after age 20 had reduced odds of developing RA compared with women whose first birth occurred at age 17 or younger (OR 0.33; 95% CI 0.16–0.66, overall p for trend 0.001; Figure 2B). Finally, the odds of developing RA in the first postpartum year were almost 4 times as high compared with subsequent years (OR 3.8; 95% CI 1.45–9.93, overall p for trend 0.004; Figure

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org

2C), all after adjustment for age, age at first birth, menarche, and number of births.

DISCUSSION

In this unique population of women with a high prevalence of RA, high fertility rates, and an increased prevalence of several known risk factors for RA, we have shown that reproductive characteristics have a significant effect on the risk of developing RA. The risk of RA onset in the post-partum period, or postpartum flare of preexisting RA, has been well described[15]. It has long been our clinical observation that the onset of RA in the postpartum period is particularly frequent in this population, perhaps because of the younger age of onset of RA in these NAN women[5,7]. This observation was confirmed, with an almost 4-fold risk of RA in the first postpartum year compared with subsequent years. No linear difference was seen in time periods beyond the first year. In a Swedish study, it was found that the postpartum period increases the risk of anticitrullinated protein antibodies (ACPA)-negative RA, but no association with ACPA-positive RA was found[13]. Because the majority (> 80%) of our NAN patients with RA were ACPA-positive[8], a differential risk would be difficult to demonstrate in this population. Our results also differed from a study of US white women, where RA risk progressively increased with increasing time since last birth[17]. A possible protective effect of fetal microchimerism was proposed. Clearly, these 2 study populations are not comparable. However, the high frequency of the shared epitope in our population would indicate a lower frequency of those HLA-DRB1 molecules that have been found to be protective for RA[18]. Assuming that fetal microchimerism does play a role in the risk of RA, it may be that the frequency of protective alleles in this homogenous NAN population is too low to have an effect. The unique genetic, environmental, and reproductive characteristics of this population will also play a role. These 3 studies illustrate that the interaction of risk factors is complex, and may not be comparable from one population to another.

The higher risk of RA conferred by the shared epitope is well known; also that 2 copies confer a greater risk than a single copy. We were unable to demonstrate any association between RA risk and the shared epitope, or any association between parity and the shared epitope as described by other investigators[17]. This is presumably due to the high prevalence of this epitope in this population. Other NAN populations, also with a high prevalence of RA, have been found to have a very high prevalence of the shared epitope in both affected and unaffected people[6,19].

As noted, NAN populations have consistently been shown to develop RA about 10 years earlier than the average onset reported for white populations[5,6,7]. Average age at the time of first pregnancy is also much earlier, at 19 years, than the 28 years reported in the general Canadian population[11], and the 25–29 years in other Western populations[20]. One can speculate that this early onset age is related to an early accumulation of collective risk factors, one of which may be early exposure to the postpartum hormonal environment. It may be that an early age at first pregnancy and RA risk are linked through some common factors leading to alterations in the local microbiome, resulting in altered host innate or adaptive immunity and leading to autoimmune conditions such as RA[21,22].

The significance of the later age of menarche adding to the risk of RA is unknown. Other studies have shown conflicting results, with some showing similar findings of a later age at menarche contributing to the risk of RA[23,24] and a recent large study finding the reverse, with an earlier age at menarche increasing the risk of RA[4]. In our study, the age of the patients with RA was somewhat older than controls; this may represent a birth cohort effect, because in North America overall the average age at menarche is decreasing[25,26], possibly because of increasing body mass index[27].

Greater parity was also clearly protective in this population with a high fertility rate, while at the same time an earlier age of first pregnancy increased the risk of RA, possibly because of an earlier age of exposure to postpartum hormonal and immunological changes. Changes in hormone levels, cytokine profiles, and immune cell function during pregnancy are complex. Serum progesterone and estrogen levels increase by 3 to 8 times during pregnancy, while plasma levels of cortisol also increase throughout pregnancy. Levels of all 3 hormones begin to fall soon after delivery. Studies suggest that the hormonal milieu induced by pregnancy appears to favor a cytokine profile that is antagonistic toward cell-mediated autoimmunity. CD4+ regulatory T cells (Tregs), essential to the maintenance of immunologic tolerance and avoidance of autoimmunity, are also key players during pregnancy and are known to increase in pregnancy and decrease postpartum[28]. Hormonal and immunological changes during pregnancy favor immune tolerance (to prevent maternal rejection of the developing fetus) and are reversed rapidly in the postpartum period. Therefore it does appear that the hormonal and immunological changes associated with pregnancy and the postpartum period represent competing risks.

There are limitations to our study. First, this is a unique population, and therefore results may not be generalizable to other populations. Second, risk factors of interest were collected retrospectively. This likely affected the accuracy of some variables, such as breastfeeding and hormonal contraception history, which we were therefore unable to include in the analysis. There is also the potential for "volunteer bias" in the control population, with women less likely to participate in the study in the immediate postpartum period, when their time is at a premium. This could create an artificial difference in the proportion of

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org

women enrolling in the study in the immediate postpartum period. Finally, we chose to combine the 2 control groups (related and unrelated healthy NAN individuals), because they did not differ in terms of age, shared epitope, parity characteristics, smoking, and educational attainment, and these were the variables of interest for this analysis. It is however possible that there are other differences between these 2 groups. In fact, because the unrelated controls were specifically excluded from participating if they had any personal or family history of autoimmune disease, it can be assumed that differences in environmental or non-shared epitope genetic risks do exist. One can speculate that these unknown differences between the control groups may have affected our results, particularly if they interact with parity. The population prevalence of known risk factors for RA in this NAN population is extremely high, and each of these risk factors has been described in other NAN populations as well, such as the high frequency of the shared epitope in both the affected and unaffected people[6,19] and the very high rates of smoking (2–3 times the rate of the general Canadian and American population)[9,10,29,30]. There appears to be an important interaction between these 2 risk factors, as recent studies suggest a gene-environment interaction between smoking and shared epitope genes, with smoking acting as a trigger for RA-specific immune reactions to citrullinated proteins[31,32]. Periodontal disease is also prevalent in this NAN group[33] as well as in many other North American indigenous groups[34,35], and may serve a similar role in promoting citrullination of autoantigens in genetically predisposed individuals[36,37,38]. Obesity is also emerging as a risk factor for RA[39], and as for the other factors listed, is very prevalent in NAN populations[40,41]. Additional genetic, biomarker, and environmental risk factors are currently being explored.

Given this concentration of known risk factors, it is perhaps surprising that the prevalence of RA is not even higher than the 2–3% reported in this population. Along with further exploration of risk factors, it is equally important to establish protective factors in this population, with parity appearing to be one such factor. As reported, additional genetic factors decrease RA risk, including the protective effect of the MMEL1-TNFRSF14 minor allele[42] and (within multicase families) an interleukin 10 promoter genotype[43]. A better understanding of factors protective of RA is warranted to understand and reduce the burden of disease in this population.

REFERENCES

1. Spector TD, Roman E, Silman AJ. The pill, parity, and rheumatoid arthritis. Arthritis Rheum 1990;33:782-9.
2. Hazes JM, Dijkmans BA, Vandenbroucke JP, de Vries RR, Cats A. Pregnancy and the risk of developing rheumatoid arthritis. Arthritis Rheum 1990;33:1770-5.
3. Heliovaara M, Aho K, Reunanen A, Knekt P, Aromaa A. Parity and risk of rheumatoid arthritis in Finnish women. Br J Rheumatol 1995;34:625-8.
4. 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;50:3458-67.
5. Barnabe C, Elias B, Bartlett J, Roos L, Peschken C. Arthritis in aboriginal Manitobans: evidence for a high burden of disease. J Rheumatol 2008;35:1145-50.
6. Peschken CA, Esdaile JM. Rheumatic diseases in North America's indigenous peoples. Semin Arthritis Rheum 1999;28:368-91.
7. Peschken CA, Hitchon CA, Robinson DB, Smolik I, Barnabe CR, Prematilake S, et al. Rheumatoid arthritis in a North American native population: longitudinal followup and comparison with a white population. J Rheumatol 2010;37:1589-95.
8. El-Gabalawy HS, Robinson DB, Hart D, Elias B, Markland J, Peschken CA, et al. Immunogenetic risks of anti-cyclical citrullinated peptide antibodies in a North American Native population with rheumatoid arthritis and their first-degree relatives. J Rheumatol 2009;36:1130-5.
9. Health Canada: Canadian Tobacco Use Monitoring Survey (CTUMS) 2009. [Internet. Accessed August 22, 2012]. Available from: http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/ctums-esutc_2009_graph-eng.php
10. Health Canada: Tobacco - First Nations, Inuit and Aboriginal Health. 2011. [Internet. Accessed August 22, 2012]. Available from: http://www.hc-sc.gc.ca/fniah-spnia/substan/tobac-tabac/index-eng.php
11. Health Canada: Changing Fertility Rates: Trends and Implications. [Internet. Accessed August 22, 2012]. Available from: http://www.hc-sc.gc.ca/sr-sr/pubs/hpr-rpms/bull/2005-10-chang-fertilit/index-eng.php
12. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
13. Bengtsson C, Orellana C, Holmqvist M, Berglund A, Wedrén S, Klareskog L, et al. Postpartum and the risk of developing rheumatoid arthritis; results from the Swedish EIRA Study [abstract]. Arthritis Rheum 2011;63 Suppl:S36.
14. Berglin E, Kokkonen H, Einarsdottir E, Agren A, Rantapaa DS. Influence of female hormonal factors, in relation to autoantibodies and genetic markers, on the development of rheumatoid arthritis in northern Sweden: a case-control study. Scand J Rheumatol 2010;39:454-60.
15. Brennan P, Silman A. Breast-feeding and the onset of rheumatoid arthritis. Arthritis Rheum 1994;37:808-13.
16. Spector TD, Silman AJ. Is poor pregnancy outcome a risk factor in rheumatoid arthritis? Ann Rheum Dis 1990;49:12-4.
17. Guthrie KA, Dugowson CE, Voigt LF, Koepsell TD, Nelson JL. Does pregnancy provide vaccine-like protection against rheumatoid arthritis? Arthritis Rheum 2010;62:1842-8.
18. Feitsma AL, van der Helm-van Mil AH, Huizinga TW, de Vries RR, Toes RE. Protection against rheumatoid arthritis by HLA: nature and nurture. Ann Rheum Dis 2008;67 Suppl 3:iii61-3.
19. Ferucci ED, Templin DW, Lanier AP. Rheumatoid arthritis in American Indians and Alaska Natives: a review of the literature. Semin Arthritis Rheum 2005;34:662-7.
20. United Nations Economic Commission for Europe, Statistical Database: Gender statistics/fertility, families and households/Mean age of women at birth of first child. (Internet. Accessed Sept 24, 2012.) Available from: http://w3.unece.org/pxweb/database/STAT/30-GE/02-Families_households/?lang=1
21. Scher JU, Abramson SB. The microbiome and rheumatoid arthritis. Nat Rev Rheumatol 2011;7:569-78.
22. Hitchon CA, El-Gabalawy HS. Infection and rheumatoid arthritis: still an open question. Curr Opin Rheumatol 2011;23:352-7.
23. Deighton CM, Sykes H, Walker DJ. Rheumatoid arthritis, HLA

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org

identity, and age at menarche. Ann Rheum Dis 1993;52:322-6.
24. Pedersen M, Jacobsen S, Klarlund M, Pedersen BV, Wiik A, Wohlfahrt J, et al. Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. Arthritis Res Ther 2006;8:R133.
25. Al-Sahab B, Ardern CI, Hamadeh MJ, Tamim H. Age at menarche in Canada: results from the National Longitudinal Survey of Children & Youth. BMC Public Health 2010;10:736.
26. Kaplowitz P. Pubertal development in girls: secular trends. Curr Opin Obstet Gynecol 2006;18:487-91.
27. Wattigney WA, Srinivasan SR, Chen W, Greenlund KJ, Berenson GS. Secular trend of earlier onset of menarche with increasing obesity in black and white girls: the Bogalusa Heart Study. Ethn Dis 1999;9:181-9.
28. Amin S, Peterson EJ, Reed AM, Mueller DL. Pregnancy and rheumatoid arthritis: insights into the immunology of fetal tolerance and control of autoimmunity. Curr Rheumatol Rep 2011;13:449-55.
29. Denny CH, Holtzman D, Cobb N. Surveillance for health behaviors of American Indians and Alaska Natives. Findings from the Behavioral Risk Factor Surveillance System, 1997-2000. MMWR Surveill Summ 2003;52:1-13.
30. Smith JJ, Ferucci ED, Dillard DA, Lanier AP. Tobacco use among Alaska Native people in the EARTH study. Nicotine Tob Res 2010;12:839-44.
31. Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum 2004;50:3085-92.
32. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38-46.
33. Schacter I, Robinson DB, Hart DM, Bertone M, Peschken CA, Smolik I, et al. Prevalence of periodontitis, anti-P. gingivalis antibodies, and rheumatoid arthritis autoantibodies in a community sample of North American natives with prevalent rheumatoid arthritis [abstract]. Arthritis Rheum 2011;63 Suppl:S301.
34. Lawrence HP. Oral health interventions among Indigenous populations in Canada. Int Dent J 2010;60 Suppl 2:229-34.
35. Mejia GC, Parker EJ, Jamieson LM. An introduction to oral health inequalities among Indigenous and non-Indigenous populations. Int Dent J 2010;60 Suppl:212-5.
36. Berthelot JM, Le Goff B. Rheumatoid arthritis and periodontal disease. Joint Bone Spine 2010;77:537-41.
37. Detert J, Pischon N, Burmester GR, Buttgereit F. The association between rheumatoid arthritis and periodontal disease. Arthritis Res Ther 2010;12:218.
38. Smolik I, Robinson D, El-Gabalawy HS. Periodontitis and rheumatoid arthritis: epidemiologic, clinical, and immunologic associations. Compend Contin Educ Dent 2009;30:188-90, 192, 194 passim; quiz 198, 210.
39. Derdemezis CS, Voulgari PV, Drosos AA, Kiortsis DN. Obesity, adipose tissue and rheumatoid arthritis: coincidence or more complex relationship? Clin Exp Rheumatol 2011;29:712-27.
40. Anand SS, Yusuf S, Jacobs R, Davis AD, Yi Q, Gerstein H, et al. Risk factors, atherosclerosis, and cardiovascular disease among Aboriginal people in Canada: the Study of Health Assessment and Risk Evaluation in Aboriginal Peoples (SHARE-AP). Lancet 2001;358:1147-53.
41. Katzmarzyk PT, Malina RM. Obesity and relative subcutaneous fat distribution among Canadians of First Nation and European ancestry. Int J Obes Relat Metab Disord 1998;22:1127-31.
42. El-Gabalawy HS, Robinson DB, Daha NA, Oen KG, Smolik I, Elias B, et al. Non-HLA genes modulate the risk of rheumatoid arthritis associated with HLA-DRB1 in a susceptible North American Native population. Genes Immun 2011;12:568-74.
43. Oen K, Robinson DB, Nickerson P, Katz SJ, Cheang M, Peschken CA, et al. Familial seropositive rheumatoid arthritis in North American Native families: effects of shared epitope and cytokine genotypes. J Rheumatol 2005;32:983-91.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Downloaded on April 19, 2024 from www.jrheum.org