Published in final edited form as:
Ann Rheum Dis. 2014 April ; 73(4): 752–755. doi:10.1136/annrheumdis-2013-203567.

Parity and the risk of developing rheumatoid arthritis: results from the Swedish EIRA study

Cecilia Orellana[(1)], **Sara Wedrén**[(2)], **Henrik Källberg**[(1)], **Marie Holmqvist**[(4)], **Elisabeth W. Karlsson**[3], **Lars Alfredsson**[(1),(5)], and **Camilla Bengtsson**[(1)] **EIRA Study Group**

[(1)]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[(2)]Rheumatology Unit, Department of Medicine, Karolinska University Hospital Solna, Stockholm, Sweden

[(3)]Brigham and Women's Hospital, Harvard Medical School, and Harvard School of Public Health, Boston, Massachusetts

[(4)]Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital Solna, Stockholm, Sweden

[(5)]Center for Occupational and Environmental Medicine, Stockholm, County Council, Sweden

Abstract

Objective—To study the impact of parity history on the risk of ACPA- (antibodies to citrullinated peptides antigens) positive/-negative rheumatoid arthritis (RA), in different age-groups.

Method—Data from a population-based case-control study of female incident RA cases were analysed (2035 cases, 2911 controls, aged 18-70). Parity history was assessed through questionnaire. Parous women were compared with nulliparous, by calculating odds ratios (OR) with 95% confidence interval (CI).

Results—Parity was associated with an increased risk of ACPA-negative RA in the age-group 18-44 (OR=2.1, 95% CI 1.4-3.2), but not in the age-group 45-70 (OR=0.9, 95% CI 0.7-1.3). Among young women, an increased risk of ACPA-negative RA was found in those with delivery during the year of symptom onset (OR=2.6, 95% CI 1.4-4.8) and at young age at first birth (<23) (OR=2.5, 95% CI 1.5-4.1).Parity and the postpartum period were not associated with ACPA-positive RA, but older age at first birth was weakly associated with a decreased risk.

Correspondence to: Cecilia Orellana, Institute of Environmental Medicine, Karolinska Institutet, Box 210, S-171 77 Stockholm, Sweden, Tel +46 8 52485474, Cecilia.orellana@ki.se.

Contributors: The Epidemiological Investigation of Rheumatoid Arthritis study group consists of: Göran Lindahl, Danderyd Hospital; Berit Sverdrup, Eskilstuna Hospital; Helena Hellström, Falu lasarett; Tomas Weitoft, Gävle Hospital; Bengt Lindell, Kalmar Hospital; Birgitta Nordmark, Johan Bratt and Ingiäld Hafström, Karolinska University Hospital; Ido Leden, Kristianstad Hospital; Björn Löfström, Katrineholm Hospital; Ann Bengtsson and Thomas Skogh, Linköping Hospital; Elisabeth Lindqvist, Lund University Hospital; Lennart Jacobsson, Malmö University Hospital; Kjell Huddénius, Rheumatology Clinic in Stockholm City; Christin Lindström, Sophiahemmet; Annika Teleman, Spenshult Hospital; Eva Baecklund and Ann Knight, Uppsala University Hospital; Olle Svernell, Västervik Hospital; Patrik Stolt, Västerås Hospital.

Conclusions—The increased risk of ACPA-negative RA in parous women of reproductive age seemed to be conferred to an increased postpartum risk and to young age at first birth. Further research is needed to explore the biological mechanisms behind our findings.

Keywords

Rheumatoid arthritis; Parity; Postpartum period; Antibodies to citrullinated peptides (ACPA); Epidemiology

INTRODUCTION

The gender difference in rheumatoid arthritis (RA) incidence is higher at reproductive ages [1-2], which might reflect a possible etiological role of hormonal factors at younger but not at older ages. A reduction in RA incidence during pregnancy, but an increase after delivery, has been described suggesting an involvement of reproductive factors in the etiology. The increased risk has been observed during the first three months up to two years postpartum [3-6], whereas parous women in the long run seem to have no increased [7-10], or even reduced risk of RA [11-13]. For other reproductive factors, such as number of children [7-9,11,13] and age at first birth [7-9,11,12], reported results are inconclusive. Notably, previous studies have been conducted without studying the two subsets of RA, characterized by the presence/absence of antibodies to citrullinated peptides (ACPA), separately.

Against this background, we aimed at studying the impact of parity history, age at first birth and the postpartum period on the risk of ACPA-positive and ACPA-negative RA, by using data from a large population-based case-control study including incident cases in Sweden.

METHOD

Study design

This study is based on the Swedish Epidemiological Investigation of RA (EIRA)comprising women aged 18-70 living in defined geographical parts of Sweden, between 1996 and 2009. The general design of EIRA has been described in detail elsewhere [14]. Briefly, incident cases of RA were included and diagnosed by rheumatologists according to the American College of Rheumatology 1987 criteria for RA [15]. Controls were randomly selected from the national population register and matched to the cases by age, gender and residential area.

Data collection

Cases and controls answered an extensive questionnaire, in order to collect information about life-style/environmental exposures, including parity, number of delivered children and year(s) when the children were born. A second version of the questionnaire was used from 2006, adding information on breastfeeding. In total, 2171 cases and 3635 controls were identified of which 2063 cases (95%) and 2911 controls (80%) answered the questionnaire. Blood samples were taken from participating cases.

Antibody assays

The blood samples were assayed for ACPA-status using the Inmunoscan-RA Mark2 ELISA test (Euro-Diagnostica, Malmo, Sweden) [16]. The cut-off was set to 25 U/ml for ACPA-positive RA. Twenty-eight cases lacked information on ACPA-status.

Exposures

For each case, the year when the first symptoms of RA occurred was defined as the index-year and the same index-year was used for the corresponding control. Since we only had information on which year the participants had given birth, parous women were defined as those who had biological offspring before or during the index-year. Women who had not given birth before or during index-year were considered as nulliparous. The postpartum period was defined as 0 (during index year), 1 year and 2 years between the most recently delivered child and the index year. Age at first birth for women aged 18-44 was categorized according to the quartiles among the controls (≤22, 23-26, 27-30 and ≥31 years).The number of children was categorized as 1, 2, 3 and ≥4.

All participants gave written informed consent and ethical approval was obtained from relevant ethical committees.

Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI) were calculated for ACPA-positive and ACPA-negative RA, associated with parity overall, number of children, age at first birth and postpartum period by means of logistic regression. Nulliparous women were used as reference group.

We adjusted for the matching variables (age and residential area). Additional adjustments for smoking (pack-years), body mass index (BMI <25/≥25), use of oral contraceptives (ever/never), breastfeeding (<24/≥24 months in total)and formal education (university degree yes/no) did not substantially change the ORs and were therefore not retained in the final analyses.

All analyses were carried out using the Statistical Analysis System (SAS) Version 9.2.

RESULTS

In total, 2035 cases and 2911 controls were included in the analyses, of which 603 cases and 906 controls were in the age of 18-44 years. In all, 64% of the cases were ACPA-positive and the mean time period between symptom onset and diagnosis was 10 months for both ACPA-positive and ACPA-negative RA (Supplementary Table 1).

Parity and risk of ACPA-positive, ACPA-negative RA

Parous women had an increased risk of developing ACPA-negative RA compared with nulliparous women in the young age-group (18-44) (OR= 2.1, 95% CI 1.4-3.2), but not in the old age-group (45-70) (OR= 0.9, 95% CI 0.7-1.3). There was no association between parity and the risk of developing ACPA-positive RA in any age-group (Table 1) nor did we

find any differences according to the number of children and the risk of ACPA-positive and ACPA-negative RA (Supplementary Table 2).

Postpartum period and risk of ACPA-positive, ACPA-negative RA

An increased risk of ACPA-negative RA was found in women, aged 18-44, who had their last child the same year as index year (OR=2.6, 95% CI 1.4-4.8). The odds ratio was lower among those with deliveries within one year before the index year (OR=1.8, 95% CI 0.9-3.6) and reached the null value within two years before disease onset (Table 2). After adjustments for age at first birth the estimates decreased.

Age at first birth and risk of ACPA-positive, ACPA-negative RA

Among women aged 18-44, the OR of ACPA-negative RA was 2.5 (95% CI 1.5-4.1) in those who had their first child before 23 years of age. The OR decreased by increasing age at first birth. A moderate decreased risk of ACPA-positive RA was found among women who had their first child after 30 years of age (OR=0.7, 95% CI 0.4-1.0) (Table 3). Adjustment for postpartum period increased the estimates for ACPA-negative RA, and decreased the estimates for ACPA-positive RA.

DISCUSSION

Our data demonstrate an increased risk of ACPA-negative RA in parous women of reproductive age (18-44), but not at older ages (45-70). The increased risk was attributable to an elevated risk during the postpartum period, and to a young age at first birth. Parity and the postpartum period were not associated with risk of ACPA-positive RA, but older age at first birth seemed to be associated with a decreased risk of this subgroup.

Our study has the advantage of being a large, population-based case-control study including incident cases. This, in combination with a high participation proportion among both cases and controls, reduced the risk of selection bias. However, some methodological considerations should be mentioned. In the postpartum analysis, misclassification of the postpartum period during index year might have occurred since we only had information on year(s) of delivery. This misclassification is probably non-differential (generally leading to a dilution of the results), which is supported by the different results for ACPA-negative and ACPA-positive RA.

The overall picture from previous literature is that parity might imply an increased risk of RA close to delivery [3-6] (with one exception showing no association [11]), but that this risk is attenuated after some years [7-13]. Our results extend these findings, by demonstrating that the increased postpartum risk was only found in ACPA-negative RA. For other reproductive factors, such as age at first birth [7-9,11,12] and number of children [7-9,11,13], previous results are inconclusive. The disparate findings might be explained by methodological issues (prevalent cases [13], inclusion of non-population-based controls [12-13]) or relatively few cases [9-13]. Notably, no previous study has investigated parity history separately for ACPA-positive and ACPA-negative RA. The finding of a decreased risk of developing ACPA-negative RA with increasing age remained even after adjustments

by smoking, BMI, use of oral contraceptives, breastfeeding and formal education. The different result observed in ACPA-positive RA remains to be elucidated.

Emerging evidences demonstrate that environmental risk factors (e.g. smoking), and genetic risk factors (e.g. HLA-DRB1shared epitope (SE) alleles) act differently in the development of ACPA-positive and ACPA-negative RA [17]. Our findings of different impact of parity history on these two subgroups thus add further evidence to the notion that RA comprises two different disease entities with different etiology.

The immunologic adaptation during pregnancy with high concentrations of different circulating hormones (e.g. cortisol, oestrogen), might explain the lower RA incidence during pregnancy [18]. After delivery the drastic fall in hormonal levels in combination with increased prolactin levels during breast-feeding might be a potential explanation to the increased postpartum risk [19]. Why these potential mechanisms act differently in the two subgroups of RA remains to be elucidated.

In summary, we found an increased risk of ACPA-negative rheumatoid arthritis in parous women of reproductive age. The increased risk was mainly due to an increased risk in the postpartum period and young age at first birth. Further research is needed in order to explore the biological mechanisms behind our findings but the effect of hormonal/reproductive factors such as the postpartum period might partly explain this notoriously higher incidence of RA in women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

First, we express our sincere gratitude to Prof.Lars Klareskog, who (together with Prof. Lars Alfredsson), is one of the principal investigators and founders of the EIRA study.We want to thank Marie-Louise Serra and Lena Nise for excellent assistance in collection of data. This study was supported by grants from the Swedish Medical Research Council, the Swedish Council for Working Life and Social Research, King Gustav V's 80-year foundation, the Swedish Rheumatic Foundation, the Stockholm County Council, the Insurance Company AFA, the Innovative Medicines Initiative-supported BTCure project, the Controlling Chronic Inflammatory Diseases with Combined Efforts project and the National Institutes of Health (NIH, AR047782).

References

1. Humphreys JH, Verstappen SM, Hyrich KL, et al. The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Ann Rheum Dis. Published Online First: 3 September 2012. 10.1136/annrheumdis-2012-201960
2. Kvien TK, Uhlig T, Odegard S, et al. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann N Y Acad Sci. 2006; 1069:212–22. [PubMed: 16855148]
3. Wallenius M, Skomsvoll JF, Irgens LM, et al. Postpartum onset of rheumatoid arthritis and other chronic arthritides: results from a patient register linked to a medical birth registry. Ann Rheum Dis. 2010; 69:332–6. [PubMed: 19717397]
4. Silman A, Kay A, Brennan P. Timing of pregnancy in relation to the onset of rheumatoid arthritis. Arthritis Rheum. 1992; 35:152–5. [PubMed: 1734904]

5. Lansink M, de Boer A, Dijkmans BA, et al. The onset of rheumatoid arthritis in relation to pregnancy and childbirth. Clin Exp Rheumatol. 1993; 11:171–4. [PubMed: 8508559]
6. Oka M. Effect of pregnancy on the onset and course of rheumatoid arthritis. Ann Rheum Dis. 1953; 12:227–9. [PubMed: 13105216]
7. Jorgensen KT, Pedersen BV, Jacobsen S, et al. National cohort study of reproductive risk factors for rheumatoid arthritis in Denmark: a role for hyperemesis, gestational hypertension and pre-eclampsia? Ann Rheum Dis. 2010; 69:358–63. [PubMed: 19289384]
8. Karlson EW, Mandl LA, Hankinson SE, et al. 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. [PubMed: 15529351]
9. Hernández Avila M, Liang MH, Willett WC, et al. Reproductive factors, smoking, and the risk for rheumatoid arthritis. Epidemiology. 1990; 1:285–91. [PubMed: 2083305]
10. Pikwer M, Bergstrom U, Nilsson JA, et al. Breast feeding, but not use of oral contraceptives, is associated with a reduced risk of rheumatoid arthritis. Ann Rheum Dis. 2009; 68:526–30. [PubMed: 18477739]
11. Guthrie KA, Dugowson CE, Voigt LF, et al. Does pregnancy provide vaccine-like protection against rheumatoid arthritis? Arthritis Rheum. 2010; 62:1842–8. [PubMed: 20309863]
12. Hazes JM, Dijkmans BA, Vandenbroucke JP, et al. Pregnancy and the risk of developing rheumatoid arthritis. Arthritis Rheum. 1990; 33:1770–5. [PubMed: 2260999]
13. Spector TD, Roman E, Silman AJ. The pill, parity, and rheumatoid arthritis. Arthritis Rheum. 1990; 33:782–9. [PubMed: 2363734]
14. Bengtsson C, Nordmark B, Klareskog L, et al. Socioeconomic status and the risk of developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis. 2005; 64:1588–94. [PubMed: 15843455]
15. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988; 31:315–24. [PubMed: 3358796]
16. Ronnelid J, Wick MC, Lampa J, et al. Longitudinal analysis of citrullinated protein/peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity and greater radiological progression. Ann Rheum Dis. 2005; 64:1744–9. [PubMed: 15843452]
17. Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. Lancet. 2009; 373:659–72. [PubMed: 19157532]
18. Straub RH, Buttgereit F, Cutolo M. Benefit of pregnancy in inflammatory arthritis. Ann Rheum Dis. 2005; 64:801–3. [PubMed: 15897301]
19. Østensen M, Villiger PM, Forger F. Interaction of pregnancy and autoimmune rheumatic disease. Autoimmun Rev. 2012; 11:437–46.

Table 1

Relative risk of ACPA-positive, ACPA-negative RA according to parity, in different age-groups. EIRA, Sweden, 1996-2006.

		18-44 years		45-70 years	
ACPA status	**Parous**	**Cases/Controls**	**OR[a] 95% CI**	**Cases/Controls**	**OR[a] 95% CI**
ACPA-negative	No	65/360	1.0	65/238	1.0
	Yes	136/546	2.1 (1.4-3.2)	458/1766	0.9 (0.7-1.3)
ACPA-positive	No	165/360	1.0	112/238	1.0
	Yes	237/546	0.9 (0.7-1.2)	797/1766	1.0 (0.8-1.2)
RA overall	No	230/360	1.0	177/238	1.0
	Yes	373/546	1.1 (0.9-1.5)	1255/1766	1.0 (0.8-1.2)

ACPA= antibodies to citrullinated peptides antigens, RA= rheumatoid arthritis, OR= odds ratio, CI= confidence interval.

[a]Adjusted by matching variables (age and residential area).

Table 2

Relative risk of developing ACPA-positive, ACPA-negative RA according to postpartum period for last delivered child in women aged 18-44. EIRA, Sweden, 1996-2006.

ACPA status	Years between last delivered child and index year	Cases/Controls	OR[a] 95% CI	OR[b] 95% CI
ACPA-negative	Nulliparous	65/360	1.0	1.0
	0	23/59	2.6 (1.4-4.8)	2.1 (0.9-4.8)
	1 year	14/57	1.8 (0.9-3.6)	1.4 (0.6-3.6)
	2 years	6/49	1.0 (0.4-2.5)	0.8 (0.2-2.3)
	P for trend[†]	-	0.0093	0.1336
ACPA-positive	Nulliparous	165/360	1.0	1.0
	0	29/59	1.1 (0.7-1.8)	0.8 (0.4-1.6)
	1 year	27/57	1.1 (0.6-1.8)	0.8 (0.4-1.5)
	2 years	20/49	0.9 (0.5-1.5)	0.6 (0.3-1.3)
	P for trend[†]	-	0.9136	0.6316

ACPA= antibodies to citrullinated peptides antigens, RA= rheumatoid arthritis, OR= odds ratio.

[a] Adjusted by matching variables (age and residential area).

[b] Adjusted by age, residential area and age at first birth.

[†] Wald chi-square test for trend.

Table 3

Relative risk of developing ACPA-positive, ACPA-negative RA according to age at first birth in women aged 18-44. EIRA, Sweden, 1996-2006.

ACPA status	Age at first birth	Cases/Controls	OR[a] 95% CI	Adjusted OR[b] 95% CI
ACPA-negative	Nulliparous	65/360	1.0	1.0
	≤22 years	39/116	2.5 (1.5-4.1)	2.7 (1.6-4.8)
	23-26 years	39/144	2.1 (1.3-3.5)	2.4 (1.3-4.4)
	27-30 years	36/156	1.8 (1.1-3.1)	2.2 (1.1-4.2)
	≥ 31 years	22/130	1.5 (0.8-2.8)	1.8 (0.8-4.0)
	P for trend[†]	-	0.0047	0.0058
ACPA-positive	Nulliparous	165/360	1.0	1.0
	≤22 years	57/116	1.0 (0.7-1.5)	0.9 (0.6-1.5)
	23-26 years	68/144	1.0 (0.7-1.4)	0.9 (0.6-1.3)
	27-30 years	67/156	0.9 (0.6-1.3)	0.8 (0.5-1.2)
	≥ 31 years	45/130	0.7 (0.4-1.0)	0.5 (0.3-1.0)
	P for trend[†]	-	0.3305	0.2339

ACPA= antibodies to citrullinated peptides antigens, RA= rheumatoid arthritis, OR= odds ratio.

[a] Adjusted by matching variables (age and residential area).

[b] Adjusted by age, residential area and years between last delivered child and the index-year.

[†] Wald chi-square test for trend.