Disease Progression in Relation to Parity among Women with Rheumatoid Arthritis

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Abstract

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Epidemiology

Women with rheumatoid arthritis (RA) often experience amelioration during pregnancy followed by a flare-up postpartum, but the relationship of pregnancy and childbirth to RA prognosis is unclear. We examined whether parity prior to RA onset was associated with longer-term disease severity and how elapsed time from birth of the last child to RA onset (latency) influenced this association. A cohort study was conducted on 222 women diagnosed with RA between 1986 and 1991, who returned for follow-up evaluation approximately 8 years later. Stratified analyses using Mantel-Haenszel methods were conducted to evaluate the association between parity and 7 specific RA severity measures based on radiographs, physical exams, and Health Assessment Questionnaires. Overall, after adjusting for age at RA onset and age at follow-up, we found limited evidence of altered risk of severe RA with respect to parity; relative risks (RR) ranged from 0.74 (95% confidence interval [CI] 0.48-1.15) for number of affected joints to 1.67 (95%

CI 0.99-2.80) for joint space narrowing. When women with non-live birth pregnancies were excluded and latency was considered, increased risk of joint erosion (RR 2.57, 95%CI 1.12-5.92) and joint space narrowing (RR 2.97, 95%CI 1.18-7.44) were observed only for parous women with deliveries <15 years prior to RA diagnosis; no increased risks were observed for the other 5 outcome measures (number of affected joints, extra-articular disease, surgery, pain, and disability). If parity is associated with disease progression, our results suggest this relationship may be complex.

Introduction

Rheumatoid arthritis is a potentially debilitating autoimmune disorder characterized by inflammation of the synovial membrane (a layer of connective tissue that lines the joint cavity, tendon sheaths, and bursae and secretes lubricating synovial fluid); production of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA); and joint deformity from cartilage and bone destruction (1). Systemic and extra-articular features can also occur such as subcutaneous nodules, vasculitis, interstitial lung disease, pleural effusion, pericarditis, splenomegaly and leukopenia. RA affects 0.5-1.0% of adults in developed countries (2), with an annualized prevalence of RA in the United States for 2001-2005 estimated at 1.5 million people (3). Like most other autoimmune diseases, RA disproportionately affects women, with incidence rates 2 to 3 times greater for women than men (4). The lifetime risk of developing RA among adults in the United States is 3.6% for women and 1.7% for men (5).

The gender disproportionality in RA patients suggests that RA risk and disease activity may be influenced by reproductive events. Several studies have shown that peak incidence rate of RA occurs among women in their late 40s and 50s (6–8), typically beyond their reproductive years. Additionally, while some studies found no relationship between parity and risk of developing RA (9,10), more studies found decreased risk of RA among parous women compared to nulliparous women (11–15). Furthermore, among RA patients, disease activity is often ameliorated during pregnancy and followed by a return or flare-up postpartum (16–18). Altogether, these possible links between RA and female reproduction suggest that pregnancy-associated immunological and/or hormonal changes play a role in the etiology, and possibly the disease course, of RA. A better understanding of how immunological and hormonal changes associated with pregnancy and

birth affect RA disease course will potentially lead to insights that could translate into better treatment for RA patients.

Among women with RA, the relationships between disease progression/severity and pre- or post-onset parity remain unclear. In one study of women with inflammatory polyarthritis (IP), of whom the majority had RA, women with at least one live birth before IP symptom onset had significantly lower Health Assessment Questionnaire (HAQ) disability scores at each follow-up anniversary compared to nulliparous women (19). However, this protective effect of parity diminished with increasing time since last delivery, and women who had a pregnancy approximately 32 years prior to IP onset had HAQ disability scores similar to nulliparous women. These findings are consistent with the earlier observed effect of parity on decreasing risk of developing RA in our data (14), suggesting a similar mechanism for disease onset and progression/severity.

The present analysis focuses on RA, excluding other forms of IP, and assesses severity of disease activity using objective assessment of radiographs and physical exam, in addition to symptomatic characteristics from HAQs of pain and disability. The purpose of our study is to determine whether parity prior to RA onset and elapsed time from birth of the last child to RA onset, hereafter referred to as latency, are associated with long-term severity of disease among women with RA.

Methods

Study Design

All study activities were approved by relevant Institutional Review Boards. We conducted a cohort study assessing RA severity in relation to pre-diagnosis parity overall and by latency.

Women in this analysis included 222 female RA cases diagnosed between November 1986 and February 1991 at ages 18-64 years and who returned for a follow-up evaluation between December 1994 and August 1999. Data were originally collected for a previous case-control study designed to assess risk of RA in relation to oral contraceptive use (20). Participants were recruited using a surveillance system involving rheumatologists, family physicians, and internists to identify newly diagnosed RA cases. To be eligible for this study, a woman had to be a resident of King County, WA or belong to Group Health Cooperative of Puget Sound, a large Seattle-based prepaid health plan. Of the potential participants identified, 93% agreed to the parent study and were examined by a board-certified rheumatologist. Following a review of the rheumatologists' physical exams, RF test results, and medical record abstracts, 319 eligible participants (87%) fit the American College of Rheumatology 1987 revised criteria for definite or probable RA (21). Of the 319 women with RA, 226 (70%) returned for the long-term follow-up evaluation. 4 women who were pregnant at RA onset were excluded because there were too few to compare to those parous or nulliparous prior to RA onset; information on the remaining 222 women were used in the present analysis.

Data Collection

Participants were interviewed in-person to collect detailed information on demographic characteristics, reproductive history, and other relevant events leading up to the first physician visit for symptoms of RA. The first visit to a physician for joint symptoms was used as the reference date for RA onset because the diagnosis of RA is sometimes delayed and patient recall of first joint symptoms may precede RA onset. Blood was collected at baseline for DNA typing to determine the presence of RA-associated HLA class II alleles. For one participant, DNA was extracted from

a mouthwash sample. Genetic predisposition for RA was modeled by counting the number of copies (0, 1, or 2) of the shared epitope, a 5-amino acid sequence motif in residues 70–74 of the HLA-DRβ chain associated with increased RA risk. For both the initial and follow-up sessions, physical examinations and clinical histories were obtained by board-certified rheumatologists at the Fred Hutchinson Cancer Research Center and the University of Washington Medical Center.

Exposure and Study Cohorts

The primary exposure evaluated was self-reported parity prior to the reference date, defined as the number of pregnancies greater than 20 weeks gestation that resulted in a live birth or stillbirth prior to the reference date for RA onset. Parity was evaluated as a dichotomous variable (0/1+), with separate analyses conducted for women with pregnancies resulting in live births only; too few stillbirths occurred for separate analyses of these events as an exposure. Pregnancies that ended in 20 weeks of gestation or less and resulted in fetal death or miscarriage can also result in immunologic and hormonal changes, which may impact RA severity; thus gravidity (number of pregnancies, regardless of outcome) prior to RA onset was also evaluated as a dichotomous variable (0/1+) for potential association with RA disease severity.

Among women who were parous at RA onset, latency was further evaluated as a dichotomous variable (<15 years/15+ years). This cut point was used because a previous study on the risk of developing RA, based on the same population as the current study, only found a protective effect of parity on risk of developing RA up to 15 years after most recent delivery (14). 15 participants (7 parous and 8 nulliparous before the reference date) had intervening deliveries between the reference date and follow-up; these were excluded in the analyses of the potential impact of latency on the association between parity and RA severity. Data from 149 parous and

58 nulliparous women with RA and no deliveries between RA onset reference date and the study follow-up date were used for this secondary analysis.

A subanalysis excluding women with non-live birth pregnancies (stillbirths, pregnancy terminations, miscarriages/spontaneous abortions, ectopic pregnancies) was conducted to compare the RA severity of parous women who only had pregnancies that resulted in live births to nulligravid women. Of the 115 study participants who fit the criteria of never having a non-live birth pregnancy, 14 participants (7 parous with only live births and 7 nulligravid before the reference date) had intervening pregnancies between the reference date and follow-up, and data on intervening pregnancies were missing for 2 participants (1 parous with only live births and 1 nulligravid before the reference date). Women with intervening pregnancies were excluded from the analyses of how latency may alter the association between gravidity and RA severity. This analysis included 59 women who only had pregnancies that resulted in live births and 40 women who had never been pregnant.

Outcome Measures

Outcomes included measures of RA severity at follow-up based on radiographs, physical exams, and HAQs. Radiographic measurements included an erosion score and a joint space narrowing score for the hands and wrists, scored by a radiologist specializing in musculoskeletal imaging, based on a method modified from Sharp, et al. (22). Erosion scores ranged from 0-170 with 170 being the most severe, and were calculated by summing the total erosion scores for 34 joints. Each joint was scored for erosions on a scale from 0-5, representing the number of erosions in that joint (0, 1, 2, 3, 4, or 5+). The 34 joints included in the total erosion score were: 8 proximal interphalangeal; R and L 1st interphalangeal; 10 metacarpophalangeal; R and L 1st metacarpal

base; R and L multangulars (trapezoid and trapezium as 1 unit); R and L scaphoid; R and L lunate; R and L triquetrum (and pisiform); R and L radius; and R and L ulna.

Joint space narrowing scores ranged from 0-144 with 144 being the most severe, and were calculated by summing the total joint space narrowing scores for 36 joints. Each joint was scored for joint space narrowing on a scale from 0-4: 0 = no joint space narrowing; 1 = focal narrowing on one side of the joint; 2 = diffuse narrowing with <50% reduction; 3 = diffuse narrowing with ≥50% reduction; 4 = joint ankyloses. The 36 joints included in the total joint space narrowing score were: 8 proximal interphalangeal; R and L 1st interphalangeal, 10 metacarpophalangeal; R and L 3rd, 4th, and 5th carpometacarpal; R and L multangular-scaphoid; R and L lunate-triquetrum; R and L capitate-scaphoid-lunate; R and L radiocarpal; and R and L radioulnar joints. Hand and wrist radiographs were obtained with an anterior-posterior and a ball catcher's (Norgaard) view for 194 (87%) of the study participants.

Measures of RA severity obtained from physical exams included affected joint count and presence of extra-articular disease. Joints were scored for swelling, loss of range of motion, and/or deformity, and involvement of a joint with any of these parameters was counted with a maximum number of affected joints of 58. The 58 joints examined consist of: 8 proximal interphalangeal joints of the hand, 2 first interphalangeal joints of the hand, 10 metacarpophalangeal, 2 wrist, 2 elbow, 2 shoulder, 18 interphalangeal joints of the foot, 8 metatarsophalangeal, 2 ankle, 2 knee, and 2 hip. The presence of extra-articular disease (none, rheumatoid nodules, lung disease, or vasculitis) was also recorded. Because none of the participants had vasculitis and only one had lung disease, the presence of extra-articular disease was evaluated as a dichotomous variable (none/1 or more condition). All participants were examined by one of two rheumatologists, who also evaluated participants for eligibility in the original parent study.

A questionnaire was administered that included dates and duration of all arthritis medication use since reference date and whether patients had undergone joint surgery due to their arthritis. Telephone interviews with the patient and with physicians' offices were used to supplement incomplete information from the questionnaire. Use of disease-modifying drugs and surgery since reference date were both evaluated as dichotomous variables (never/ever). However, the use of these drugs was assessed as a potentially modifying factor, rather than an outcome, due to the widespread practice of initiating their use immediately upon diagnosis during the time women were in the study were diagnosed. HAQs were also administered to each participant; 207 (93%) completed the Pain Index, and 209 (94%) completed the Disability Index (23). Both indices were on a scale ranging from 0-3, with 3 being the most severe.

We also counted the total number of severe outcomes present for the following measures: erosion score on radiographs of hands and wrists, joint space narrowing score on radiographs of hands and wrists, number of joints affected on physical exam, presence of extra-articular disease, whether or not joint surgery was performed, disability index from the HAQ, and pain index from the HAQ. The total number of severe outcomes for each participant ranged from 0 to 7.

Standard thresholds for determining mild, moderate, or severe RA have not been established; thus, continuous outcome variables were categorized into tertiles (mild, moderate, or severe) based on the nulliparous participants' distributions. Continuous outcome variables were then dichotomized for analysis (not severe; lower 2 tertiles/severe; top tertile). The cut points for the severe category in these continuous variables were: erosion score >31, joint space narrowing score >15, affected joint count >11, HAQ pain score >1.1., HAQ disability score >0.625, and total number of severe outcomes >2. In a subanalysis excluding participants with non-live birth pregnancies, the severity cut points were: erosion score >33, joint space narrowing score >20,

affected joint count >12, HAQ pain score >0.9, HAQ disability score >0.625, total number of severe outcomes >2.

Data Analysis

A stratified analysis using Mantel-Haenszel methods was conducted to calculate relative risk (RR) estimates and 95% confidence intervals (CIs) to evaluate the association between parity as a dichotomous variable (nulliparous/parous) and dichotomized RA disease severity (not severe/ severe) measures for all metrics. The parous participants were further categorized by latency (<15 years/15+ years) to assess how latency may modify the association between parity and RA disease severity. Socioeconomic and demographic variables evaluated for their potential effects on the relationships of interest included characteristics at the reference date: age at onset of RA (16-24, 25-34, 35-44, 45-54, or 55-64 years); education level (grade school, high school, technical school, college, graduate school, or other); annual household income (<15k, 15k-30k, 30k-45k, or >45k $); race/ethnicity (American Indian or Alaska Native, Asian, Black, Hispanic, White,); and ever married (yes/no). Because very few of the participants self-identified with each of the racial/ethnic minority categories (5.4% Asian, 2.3% Black, 2.7% Hispanic, 4.1% American Indian or Alaska Native), race/ethnicity was recategorized for this analysis as a dichotomous variable (Non-Hispanic White/People of Color). Participants' health and reproductive characteristics prior to RA onset that were evaluated for potential confounding include: number of pregnancies (0, 1, 2, 3, or 4+); number of pregnancies that resulted in live births (0, 1, 2, 3, or 4+), number of pregnancies that ended in <20 weeks of gestation (0, 1, or 2+), oral contraceptive use (never/ever), whether periods had stopped permanently (yes/no), smoking status (never, current, or former), and body mass index (<18.5, 18.5-24.9, 25.0-29.9, or ≥30.0). Elapsed years from onset to follow-up (<6.0,

6.0-8.9, 9.0-11.9, or 12.0+) and age at follow-up (16-24, 25-34, 35-44, 45-54, 55-64, or 65-74 years) were also assessed for their potential effects. Of these characteristics, only age at RA onset and age at follow-up were also associated with parity and two RA severity outcome—joint count and extra-articular disease. Adjusting for either age at RA onset or age at follow-up resulted in a risk estimate with a greater than 10% difference from our crude RR in some of the outcomes of interest, so both were adjusted for in final analyses for all outcomes.

We also explored each of the following variables separately for their possible effects on the relationships: whether or not joint surgery was performed (never/ever), use of disease-modifying anti-rheumatic drugs (never/ever), presence of RA-associated HLA alleles (0, 1, or 2 copies of the shared epitope), and RF (negative/positive). The number of women who had never used disease-modifying anti-rheumatic drugs and the number of women who had ever had joint surgery were too small to stratify by these variables. The RRs were similar across all strata for RF and the shared epitope; thus stratified results are not included in the final risk estimates.

In order to further distinguish the effect of parity on RA outcome from the potential effects of pregnancies that were not carried to term or resulted in a stillbirth, a subanalysis was conducted to compare the RA severity of women who only had live births to that of nulligravid women. Cut points for stratifying continuous outcomes were established using tertiles (mild, moderate, or severe) calculated from the nulligravid participants. As in the primary analysis, risk estimates and 95% CIs were adjusted for both age at RA onset and age at follow-up, and the potential impact of latency on risk estimates was evaluated. To account for potential RA onset year cohort effects, additional exploratory analyses were conducted adjusting for either reference year of RA onset or years from RA onset to follow-up, categorized into tertiles.

Results

222 women with RA were evaluated a median of 8.3 years after onset of RA (range 4.4-19.8 years) (data not shown). Of these, 156 (70.3%) were parous prior to RA onset, and 66 (29.7%) were nulliparous. At RA onset, the parous women were more likely to be older and less well-educated (Table 1). Parous women were also more likely to have been married, be post-menopausal, and have quit smoking prior to RA onset compared to nulliparous women (Table 2). A slightly greater proportion of parous women had 0 copies of the shared epitope, whereas a slightly greater proportion of nulliparous women had 2 copies of the shared epitope (Table 3). The parous and nulliparous participants did not differ significantly in the serologic (RF) features of RA assessed in this study. The median elapsed time between the RA onset and the study follow-up date was 8.3 years (range 4.4-19.8 years) for the parous participants and 8.0 years (range 4.8-15.9 years) for the nulliparous participants (data not shown). The participants did not differ much by parity in time to follow-up, but the parous women were more likely to be older at the follow-up date (Table 3).

In the time between RA onset and study follow-up, 10 parous women and 10 nulliparous had intervening pregnancies (Table 3). Of the 10 parous women with intervening pregnancies: 7 women had pregnancies that resulted in a single live birth; 3 women had a combination of spontaneous abortions or miscarriages, induced abortions, and ectopic pregnancies. Of the 10 nulliparous women with intervening pregnancies: 6 women only had pregnancies that resulted in live births; 3 women had a combination of live births, spontaneous abortions or miscarriages, induced abortions, and ectopic pregnancies; 1 woman had missing data (data not shown).

Parous RA patients did not have markedly increased or decreased risks of any of the measures of disease severity assessed in this study (Table 4). However, the RRs were increased

and the lower CI was close to 1 for several outcomes: joint space narrowing (RR 1.67, 95%CI 0.99-2.80), HAQ disability score (RR 1.38, 95%CI 0.94-2.02), and total number of severe outcomes (RR 1.57, 95%CI 0.99-2.51). Exclusion of women with pregnancies that resulted in non-live birth and/or assessing gravidity as the exposure did not change these risk estimates (data not shown).

When parous women were stratified by latency, there was no evidence that RRs for the various RA severity outcomes differed markedly by latency (Table 5). Among women who never had a pregnancy that resulted in a non-live birth and excluding women with intervening pregnancies, women who had a live birth within 15 years before RA onset were more than twice as likely to have a severe erosion score (RR 2.57, 95%CI 1.12-5.92), a severe joint space narrowing score (RR 2.97, 95%CI 1.18-7.44), and a greater number of total severe outcomes (RR 2.21, 95%CI 1.04-4.70) compared to nulligravid women. No increased or decreased risk of any outcome was observed for women with a latency of 15+ years compared to nulligravid women, except for having a fewer number of affected joints (RR=0.46, 95% CI: 0.26-0.82). Adjusting for reference year of RA onset or elapsed years from RA onset to follow-up did not alter RRs for any of the severity measurements.

Discussion

The epidemiologic evidence for the possible effects of parity on RA development is inconsistent. Some studies have found parity to be protective against developing RA (11–15) whereas others observed no relationship (9,10). One possible explanation for inconsistent findings is that any effect of parity may decrease over time. A recent study based on the case-control data used in the current analysis observed a protective effect of parity (but not gravidity without parity)

on development of RA that decreased with longer elapsed time since a woman's most recent delivery (14). If risk factors for developing RA are also responsible for the progression of RA severity, we would expect parous women to have less severe disease then nulliparous women and for this protective effect of parity to decrease with increasing latency.

In contrast, the current analysis demonstrated very limited evidence of altered risk of severe RA progression with respect to parity before RA onset or latency. After excluding any women with non-live birth pregnancies, for only 3 outcomes (erosion score, joint space narrowing, and joint count) of the 7 specific outcomes examined was there an association with parous status, and not in the direction expected if having live births with a short latency confers protection against disease progression. This is inconsistent with a hypothesis that parity improves RA prognosis; in fact, our data suggest the opposite.

There are several limitations to our study, so these results must be interpreted cautiously. Because of sample size constraints, we were unable to assess how the following variables may affect the relationship between parity and RA severity: type of disease-modifying drugs and the duration they were taken; type of surgery and when it was performed; intervening pregnancies; and adverse pregnancy outcomes. Future studies of RA prognosis with more detailed information on exposures between RA onset and follow-up assessments of RA severity are warranted.

When the exposure of parity was refined to exclude non-live birth pregnancy, our results suggest that women with a latency <15 years had an increased risk of severity for selected RA outcomes (erosion score, joint space narrowing score, and total number of severe outcomes) compared to nulligravid women, and women with a latency of 15+ years had a decreased risk of severity for one RA outcome (joint count) compared to nulligravid women. Two biological explanations may be considered for why women with greater latency appear to have better

prognoses than women with lower latency: an RA onset year cohort effect and/or an effect of treatment. However, adjusting for RA onset year had no effect on the risk of severe outcomes, and we did not have the numbers to evaluate any effect of joint surgery or use of disease-modifying anti-rheumatic drugs on the association between parity and RA severity, though exclusion of women who did not use drugs or who had surgery did not alter these results. It is possible that, for some reasons unknown, treatments may have been prescribed differently for women with and without live births, and our inability to account for this may be at least responsible for these results.

Another possible explanation for our results is the differential effect of the maternal immune response to different paternal/fetal HLA antigens (24). During pregnancy, cells are exchanged from mother to fetus and fetus to mother across the placenta (25). Some of these cells can persist in their respective hosts for decades after parturition (26). Retention of a small quantity of cells originating from a genetically distinct individual is termed 'microchimerism' (Mc) (27). Mc of fetal origin (FMc) persisting in the mother may impact long-term maternal health, either directly or by sustaining a maternal immune response to the FMc (28). It is possible that a women negative for the shared epitope may be exposed to RA risk alleles via pregnancy and FMc, thus increasing her risk of developing severe RA (29,30). We observed no difference in RA severity risk between parous and nulliparous patients by the number of copies of the shared epitope they possess. However, to truly evaluate the potential effect of FMc on RA severity, genetic data of all the participants' offspring must be collected.

In summary, overall, we observed no difference in risk of developing severe RA by parity. However, there was a suggestion that having a live birth prior to diagnosis may be associated with increased occurrence of selected severity outcome measures for women with <15 years elapsed time between her last delivery and RA onset. Although a woman's reproductive history may

influence her risk of developing RA, the relationship of parity with long-term RA prognosis appears to be complex.

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Table 1: Participant socioeconomic and demographic characteristics by parity at RA onset

	Parous (n=156)		**Nulliparous** (n=66)	
Characteristic	n	(%)	n	(%)
Age				
16-24	2	(1.3)	13	(19.7)
25-34	16	(10.3)	23	(34.8)
35-44	43	(27.6)	18	(27.3)
45-54	46	(29.5)	8	(12.1)
55-64	49	(31.4)	4	(6.1)
Education				
Grade School	17	(10.9)	1	(1.5)
High School	63	(40.4)	22	(33.3)
Technical School	23	(14.7)	18	(27.3)
College	53	(34.0)	25	(37.9)
Household Income				
< $15k	20	(12.8)	10	(15.2)
$15k-$30k	45	(28.9)	20	(30.3)
$30k-$45k	39	(25.0)	18	(27.3)
> $45k	44	(28.2)	16	(24.2)
Missing	8	(5.1)	2	(3.0)
Race/Ethnicity				
Non-Hispanic White	135	(86.5)	55	(83.3)
People of Color	21	(13.5)	11	(16.7)
Ever Married				
Yes	124	(79.5)	32	(48.5)
No	32	(20.5)	34	(51.5)

Table 2: Participant reproductive and health characteristics by parity prior to RA onset

	Parous (n=156)		Nulliparous (n=66)	
Characteristic	n	(%)	n	(%)
Gravid				
No			48	(72.7)
Yes			18	(27.3)
# of Pregnancies (gravidity)				
1	17	(10.9)	12	(66.6)
2	43	(27.6)	3	(16.7)
3	40	(25.6)	2	(11.1)
4+	56	(35.9)	1	(5.6)
# of Pregnancies > 20 weeks (parity)				
1	29	(18.6)		
2	52	(33.3)		
3	41	(26.3)		
4+	34	(21.8)		
# of Live Births				
1	29	(18.6)		
2	52	(33.3)		
3	43	(27.6)		
4+	32	(20.5)		
# of Stillbirths				
0	152	(97.4)		
1	4	(2.6)		
# of Pregnancy Terminations				
0	133	(85.3)	54	(81.8)
1	18	(11.5)	7	(10.6)
2+	5	(3.2)	5	(7.6)
# of Miscarriages/Spontaneous Abortions				
0	108	(69.2)	59	(89.4)
1	40	(25.6)	6	(9.1)
2+	8	(5.1)	1	(1.5)
# of Ectopic Pregnancies				
0	151	(96.8)	66	(100.0)
1	5	(3.2)	0	(0.0)
Oral Contraceptive Use				
Never	45	(29.0)	20	(30.3)
Ever	110	(71.0)	46	(69.7)
missing	1			
Periods stopped permanently				
No	74	(47.4)	56	(15.2)
Yes	82	(52.6)	10	(84.8)
Body Mass Index				
Underweight (< 18.5)	6	(3.8)	5	(7.6)
Normal (18.5-24.9)	97	(62.2)	36	(54.5)
Overweight (25.0-29.9)	31	(19.9)	13	(19.7)
Obese (30.0+)	22	(14.1)	12	(18.2)
Smoking Status				
Never	63	(40.4)	39	(59.1)
Current	43	(27.6)	15	(22.7)
Former	50	(32.1)	12	(18.2)

Table 3: Genetic and serological features of RA and intervening characteristics between RA onset and study follow-up by parity

	Parous (n=156)		Nulliparous (n=66)	
Characteristics	n	(%)	n	(%)
Copies of Shared Epitope				
0	54	(34.6)	16	(24.2)
1	73	(46.8)	34	(51.5)
2	29	(18.6)	16	(24.2)
Rheumatoid Factor at Diagnosis				
Positive	81	(51.9)	35	(53.0)
Negative	75	(48.1)	31	(47.0)
Disease-Modifying Anti-Rheumatic Drugs				
Never Used	33	(21.2)	14	(21.2)
Used, < 12 months	19	(12.2)	6	(9.1)
Used, 12-23 months	11	(7.1)	8	(12.1)
Used, ≥ 24 months	79	(50.6)	32	(48.5)
Used, unknown duration	14	(9.0)	6	(9.1)
Age at Follow-Up				
16-24	0	(0.0)	1	(1.5)
25-34	3	(1.9)	16	(24.2)
35-44	19	(12.2)	25	(37.9)
45-54	45	(28.9)	16	(24.2)
55-64	49	(31.4)	5	(7.6)
65-74	40	(25.6)	3	(4.6)
Additional Pregnancies (gravidity)				
Yes	10	(6.5)	10	(15.6)
No	145	(93.5)	54	(84.4)
missing	1		2	
Additional Births (parity)				
Yes	7	(4.5)	8	(12.1)
No	149	(95.5)	58	(87.9)

Table 4: Risk of developing severe RA for parous women relative to nulliparous women

	Parous (n=156)		Nulliparous (n=66)		Adjusted RR*	95% CI
Outcome	**n**	**(%)**	**n**	**(%)**		
Erosion Score (>31)	50/137	(36.5)	17/57	(29.8)	1.07	(0.65-1.78)
Joint Space Narrowing (>15)	62/137	(45.3)	18/57	(31.6)	1.67	(0.99-2.80)
Joint Count (>11)	50/156	(32.1)	21/66	(31.8)	0.74	(0.48-1.15)
Extra-Articular Disease	28/155	(18.1)	6/66	(9.1)	1.21	(0.58-2.54)
Surgery	28/154	(18.2)	10/65	(15.4)	1.27	(0.59-2.73)
HAQ Pain Score (>1.1)	62/144	(43.1)	19/63	(30.2)	1.24	(0.77-1.99)
HAQ Disability Score (>0.625)	74/146	(50.7)	21/63	(33.3)	1.38	(0.94-2.02)
Total Severe Outcomes (>2)	57/126	(45.2)	16/56	(28.6)	1.57	(0.99-2.51)

* adjusted for age at RA onset and age at follow-up for all outcomes

Table 5: Risk of developing severe RA for parous women, stratified by latency, relative to nulliparous women overall and only among women who never had a non-live birth pregnancy

		All Participants					Excluding Women with Non-Live Birth Pregnancies				
		Severe RA Outcome			Adjusted RR*	95% CI	Severe RA Outcome			Adjusted RR*	95% CI
Outcome	**Latency**	**N**	**n**	**(%)**			**N**	**n**	**(%)**		
Erosion Score	Nulliparous	50	14	(28.0)	1.00	ref	35	12	(34.3)	1.00	ref
	< 15 years	36	13	(36.1)	1.82	(0.95-3.50)	16	10	(62.5)	2.57	(1.12-5.92)
	15+ years	95	34	(35.8)	0.91	(0.48-1.73)	33	10	(30.3)	0.41	(0.13-1.25)
Joint Space Narrowing	Nulliparous	50	16	(32.0)	1.00	ref	35	12	(34.3)	1.00	ref
	< 15 years	36	15	(41.7)	1.53	(0.87-2.70)	16	11	(68.8)	2.97	(1.18-7.44)
	15+ years	95	43	(45.3)	1.35	(0.64-2.85)	33	10	(30.3)	1.01	(0.18-5.59)
Joint Count	Nulliparous	58	19	(32.8)	1.00	ref	40	15	(37.5)	1.00	ref
	< 15 years	43	9	(20.9)	0.88	(0.43-1.78)	20	8	(40.0)	1.15	(0.54-2.48)
	15+ years	106	39	(36.8)	0.77	(0.48-1.24)	39	17	(43.6)	0.46	(0.26-0.82)
Extra-Articular Disease	Nulliparous	58	6	(10.3)	1.00	ref	40	5	(12.5)	1.00	ref
	< 15 years	43	5	(11.6)	1.19	(0.40-3.53)	20	5	(25.0)	1.89	(0.68-5.25)
	15+ years	106	21	(19.8)	1.10	(0.51-2.37)	39	9	(23.1)	0.82	(0.33-2.01)
Surgery	Nulliparous	57	10	(17.5)	1.00	ref	40	8	(20.0)	1.00	ref
	< 15 years	43	8	(18.6)	2.29	(0.79-6.68)	20	6	(30.0)	2.58	(0.74-9.04)
	15+ years	105	20	(19.0)	0.95	(0.36-2.54)	38	7	(18.4)	0.60	(0.12-2.89)
HAQ Pain Score	Nulliparous	56	17	(30.4)	1.00	ref	39	13	(33.3)	1.00	ref
	< 15 years	40	19	(47.5)	1.15	(0.70-1.90)	19	12	(63.2)	1.53	(0.84-2.78)
	15+ years	97	42	(43.3)	1.21	(0.63-2.31)	36	22	(61.1)	0.93	(0.49-1.77)
HAQ Disability Score	Nulliparous	56	17	(30.4)	1.00	ref	39	12	(30.8)	1.00	ref
	< 15 years	41	16	(39.0)	1.16	(0.69-1.95)	20	9	(45.0)	1.21	(0.62-2.39)
	15+ years	98	53	(54.1)	1.47	(0.91-2.37)	36	24	(66.7)	1.58	(0.80-3.10)
Total Severe Outcomes	Nulliparous	49	14	(28.6)	1.00	ref	35	12	(34.3)	1.00	ref
	< 15 years	33	12	(36.4)	1.66	(0.87-3.17)	15	10	(66.7)	2.21	(1.04-4.70)
	15+ years	88	41	(46.6)	1.54	(0.89-2.67)	31	12	(38.7)	0.78	(0.34-1.81)

*Adjusted for age at RA onset and age at follow-up for all outcomes