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Disease Progression in Relation to Pre-Onset Parity among Women with Rheumatoid Arthritis

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Abstract

Objective.—Rheumatoid arthritis (RA) often ameliorates during pregnancy and flares postpartum, but the relationship of pregnancy and childbirth to RA prognosis is unclear. We examined RA severity for association with parity prior to RA onset and asked whether time from birth (latency) and/or the mother's HLA genotype influenced results.

Methods.—A cohort study was conducted of 222 women previously identified in a prospective study of newly diagnosed RA, who returned for follow-up evaluation a median of 8 years later. Stratified analyses using Mantel-Haenszel methods were conducted to evaluate 5 RA severity measures including hand and wrist radiographs, physical exams, and Health Assessment Questionnaires for association with parity.

Results.—Overall we observed little evidence of altered risk of progression to severe RA in relation to pre-onset parity, adjusting for RA onset age and time to follow-up. Stratifying parous women who had only live births by latency (<15 years/15+ years) showed no difference in risk of severe RA compared to nulligravid women. Live birth deliveries were significantly protective for women with 0 but not for those with 1+ copies of the RA risk-associated HLA-DRB1 shared epitope sequence for erosion score (RR 0.26 95% CI 0.09–0.89) and joint count (RR 0.28 95% CI 0.09–0.87).

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Conclusion.—We observed little evidence of difference in severe RA by pre-onset parity overall. However, among women not predisposed to RA by possessing the risk-associated HLA genotype, parous women who had only live births had lower risk of progression to severe RA as measured by erosion score and joint count.

Keywords

rheumatoid arthritis; parity

1. Introduction

Gender disproportionality in rheumatoid arthritis (RA) occurrence suggests that risk, disease progression, and severity may be influenced by reproductive events [1–4]. Whereas some studies found no relationship between parity and RA risk [5,6], more studies report decreased RA risk among parous compared to nulliparous women [7–11]. Furthermore, disease activity is often ameliorated during pregnancy but returns postpartum [12,13]. Altogether, these observations suggest pregnancy-associated changes play a role in RA onset, and possibly disease course.

Among women with RA, relationships between disease progression/severity and pre- or post-onset parity remain unclear. One study found, among parous women, increasing parity was associated with greater RA severity determined by clinical evaluation, radiological score, biological inflammation, and presence of HLA alleles associated with RA [14]. Another reported non-significant trends of less radiographic damage and disability, as measured by Health Assessment Questionnaire (HAQ), in women with more pregnancies [15]. In a study of women with inflammatory polyarthritis, the majority with RA, women with ≥1 live birth before symptom onset had significantly lower HAQ disability scores at each follow-up anniversary compared to nulliparous women [16]. However, this protective effect of parity diminished with increasing time since last delivery, and women who had a pregnancy 32+ years prior to onset had HAQ disability scores similar to nulliparous women. That symptoms differed by elapsed time since pregnancy is consistent with results of a study reporting a decreased risk of developing RA in relation to parity that diminished with time since last delivery [10], potentially suggesting a similar mechanism for disease onset and progression/severity.

The present analysis focuses on RA and assesses disease severity using objective assessments (radiographs and physical exam) and symptomatic characteristics (pain and disability HAQs). The purpose of our study was to determine whether parity prior to RA onset is associated with long-term severity of disease among women with RA as well as whether elapsed time from delivery of the last child to RA onset (hereafter referred to as latency) and mother’s RA risk-associated HLA genotype modify this relationship.

2. Methods

2.1 Study Design and Data Collection

We conducted a cohort study evaluating RA severity (assessed by clinical exam, radiographic measures, and HAQs at follow-up) in relation to pre-onset parity (0/1+ deliveries at 20+ weeks gestation). This analysis included 222 female RA cases diagnosed November 1986-February 1991 at ages 18–64 years who returned for follow-up evaluation December 1994-August 1999. Initial identification of RA cases was described previously [17]. Briefly, 319 participants in the initial study met the American College of Rheumatology 1987 criteria for RA [18]. 226 (71%) returned for follow-up evaluation. 4 women, who were pregnant at RA onset, were excluded; the remaining 222 women were included in the present analysis. Additional analyses of the potential modifying effects of latency (elapsed time from delivery of last child to RA onset) and HLA genotype (0, 1, or 2 copies of the RA risk-associated shared epitope) on the relationship between RA severity and pre-onset parity were conducted on a subset of the study population that excluded women with non-live birth pregnancies. This study was approved by the University of Washington and Fred Hutchinson Cancer Research Center Institutional Review Boards.

Participants were interviewed in-person for demographic characteristics, reproductive history, and relevant events prior to their first physician visit for RA symptoms. First physician visit for joint symptoms was used as the reference date for RA onset because diagnosis of RA is sometimes delayed, and patient recall of first joint symptoms may precede RA onset.

Standardized RF tests were conducted at the University of Washington. At the time of initial data collection, testing for anti-citrullinated protein antibodies (ACPA) had not yet been introduced into clinical practice. Therefore, before conducting the current analyses we obtained archived serum samples for ACPA testing (QUANTA Lite® CCP3.1 IgG/IgA ELISA). HLA class II genotyping was also conducted for measuring genetic predisposition for RA as modeled by number of copies (0, 1, or 2) of the shared epitope, an HLA-DRB1 sequence associated with increased RA risk.

The follow-up evaluation included: a questionnaire detailing medical and reproductive history in the intervening time since RA onset; a physical examination, including standardized joint count; hand and wrist radiographs; medical record abstraction; and self-administered pain and disability HAQs. Hand and wrist radiographs were obtained with anterior-posterior and ball catcher's (Norgaard) views for 194 (87%) of study participants. At both the initial and follow-up sessions, all physical examinations and clinical histories were obtained by the 2 board certified study rheumatologists.

2.2 Exposure and Study Cohorts

The primary exposure was self-reported parity, defined as the number of pregnancies that lasted 20+ weeks gestation, resulting in a live birth or stillbirth prior to the reference date for RA onset, and dichotomized as 0/1+; too few stillbirths occurred for separate analyses. Pregnancies that ended in <20 weeks gestation and resulted in fetal death or miscarriage could also impact RA severity, albeit differently than pregnancies carried to term; thus

gravidity (number of pregnancies, regardless of outcome) prior to RA onset was also evaluated as a dichotomous variable (0/1+).

To account for potential effects of gravidity without parity, analyses of latency and HLA genotype excluded women with non-live birth pregnancies (stillbirths, pregnancy terminations, miscarriages/spontaneous abortions, ectopic pregnancies) and compared RA severity of parous women who only had pregnancies that resulted in live births to nulligravid women. Of 137 women who fit the criteria of never having a non-live birth pregnancy, 11 had intervening pregnancies between onset and follow-up (3 parous with only live births, 8 nulligravid before onset). Women with intervening pregnancies were excluded from analyses of how latency may alter the association between gravidity and RA severity. This analysis included 126 women, 86 who only had pregnancies that resulted in live births and 40 who had never been pregnant.

Among women who had only live birth deliveries prior to RA onset, latency was evaluated as a dichotomous variable (<15 years/15+ years from last delivery to disease onset). This cut point was used because prior work on RA in this same population observed a protective effect of parity on risk of RA up to 15 years after the most recent delivery [10]. RA-associated HLA genotype was also evaluated (0, 1, or 2 copies of the shared epitope).

2.3 Outcome Measures

Outcomes included measures of RA severity at follow-up based on radiographs, physical exams, and HAQs. Radiographic measurements included erosion score and joint space narrowing score for hands and wrists, scored by a radiologist specializing in musculoskeletal imaging, based on a method modified from Sharp, et al. [19]. Erosion scores ranged from 0–170 with 170 being the most severe and were calculated by summing erosion scores for 34 joints: 8 proximal interphalangeal; right and left (R&L) 1st interphalangeal; 10 metacarpophalangeal; R&L 1st metacarpal base; R&L multangulars (trapezoid and trapezium as 1 unit); R&L scaphoid; R&L lunate; R&L triquetrum (and pisiform); R&L radius; and R&L ulna. 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+).

Joint space narrowing scores ranged from 0–144 with 144 being the most severe and were calculated by summing joint space narrowing scores for 36 joints: 8 proximal interphalangeal; R&L 1st interphalangeal, 10 metacarpophalangeal; R&L 3rd, 4th, and 5th carpometacarpal; R&L multangular-scaphoid; R&L lunate-triquetrum; R&L capitate-scaphoid-lunate; R&L radiocarpal; and R&L radioulnar 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).

Measures of RA severity obtained from physical exams included affected joint count. 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 consisted 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.

HAQs were administered to each participant; 207 (93%) completed the Pain Index, and 209 (94%) completed the Disability Index [20]. Both indices were scaled from 0–3, with 3 being the most severe.

Standard thresholds for 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, and subsequently further dichotomized for analysis (not severe, lower 2 tertiles/severe, top tertile). Cut points for the severe category were: erosion score >31, joint space narrowing score >15, affected joint count >11, HAQ pain score >1.1, and HAQ disability score >0.625. In the analyses excluding participants with non-live birth pregnancies, severity cut points changed slightly when using nulligravid participants as a reference: erosion score >33, joint space narrowing score >20, affected joint count >12, HAQ pain score >0.9, and HAQ disability score >0.625.

2.4 Data Analysis

Stratified analysis using Mantel-Haenszel methods [21] 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. Parous participants were further categorized by latency (<15 years/15+ years) or number of copies of the RA risk-associated shared epitope (0, 1, or 2) to assess how these variables may modify the association between parity and RA disease severity. Socioeconomic and demographic variables evaluated for potential effects on the relationships of interest included characteristics at the reference date: age at RA onset (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 dollars); race/ethnicity (American Indian or Alaska Native, Asian, Black, White, Hispanic); and ever married (yes/no). Because very few participants self-identified with each racial/ethnic minority category (5.4% Asian, 2.3% Black, 2.7% Hispanic, 4.1% American Indian or Alaska Native), race/ethnicity was categorized as Non-Hispanic White/People of Color. Participants' health and reproductive characteristics prior to RA onset evaluated for potential confounding included: 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/ever), 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 potential effects.

Due to the increasingly common practice of initiating medication use at diagnosis during the time women in the study were diagnosed, drug use was assessed as a potentially modifying factor. Use of medications for RA was recorded both on the physical exam (medications taken prior to and at the time of the physical) and in detail on the questionnaire (including dates and duration of arthritis medications used since onset). Telephone interviews with

patients and physicians' offices were used to supplement incomplete questionnaire information. DMARD use was documented for sulfasalazine, oral gold, gold shots, methotrexate, hydroxycholorquine, cloroquine, D-penicillamine, cyclophosphamide, azathioprine, etanercept, cyclosporine, and leflunomide and evaluated as a dichotomous variable (0–5 months used/≥6 months used). We also evaluated RF (negative/positive) and ACPA (negative/positive) for their possible effects on the relationship between parity and RA severity.

To further distinguish the effect of parity on RA severity from potential effects of pregnancies that were not carried to term or resulted in a stillbirth, a subanalysis was conducted to compare 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 nulligravid participants. As in the primary analysis, risk estimates and 95% CIs were adjusted for age at RA onset and at follow-up, and potential impacts of latency or RA risk-associated HLA alelles on risk estimates were 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.

3. Results

156/222 (70.3%) women with RA were parous prior to RA onset. Among nulliparous women, 18/66 (27.3 %) had been pregnant before (Table 1). At RA onset, parous women were more likely to be older and have ever been a smoker compared to nulliparous women, but there was no difference in race/ethnicity or oral contraceptive use (Table 1). Compared to nulliparous women, parous women were more likely to be less well-educated, have been married, or be post-menopausal, but did not differ markedly by household income, race/ethnicity, or number of pregnancies that ended in <20 weeks of gestation (data not shown). Adjusting for either age at 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; however, after adjusting for age at onset and age at follow-up, the relationship of interest between parity and RA severity was not substantially changed with ever being a smoker, education, marital status, or being post-menopausal (data not shown). Therefore, only age at onset and age at follow-up were adjusted for in final analyses for all outcomes.

The median elapsed time between RA onset and the follow-up date was 8.3 years for parous and 8.0 years for nulliparous participants (data not shown). Although all RA diagnoses were during the same time period, the time range between onset and follow-up was variable because RA onset was defined as the first physician visit for joint symptoms and diagnosis was sometimes delayed. The range was similar for parous and nulliparous women (4.4–19.8 and 4.8–15.9 years, respectively). Although participants did not differ substantially by parity at time to follow-up, parous women were more likely to be older at the follow-up date (Table 2). Parous and nulliparous participants did not differ by RF or ACPA status, whether they had ever taken DMARDs, nor the duration of DMARD use (Table 2). RF, ACPA, and use of DMARDS for ≥6 months did not substantively affect the relationship between parity and RA severity (data not shown), so they were not included in the final analyses.

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

Overall, parous RA patients did not have markedly increased or decreased risks of severe RA by any of our outcome measures, adjusting for age at RA onset and age at follow-up. However, 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) and HAQ disability score (RR 1.38, 95% CI 0.94–2.02). Exclusion of women with any pregnancies resulting in non-live birth slightly decreased risk estimates for all the severity outcomes, but the CI included 1 for all but one outcome measure. Among women with only live birth pregnancies, parous women had significantly decreased risk of having a severe outcome for joint count compared to nulligravid women (RR 0.55, 95% CI 0.33–0.92). (Table 3)

Exclusion of women with non-live birth pregnancies and stratifying parous women by latency (<15 years/15+ years) showed no difference in risk of severe RA by parity after adjusting for age at RA onset and age at follow-up (Table 4). Adjusting for reference year of RA onset or elapsed years from onset to follow-up did not alter RRs for any of the severity measurements (data not shown).

Excluding women with non-live birth pregnancies and stratifying by RA risk-associated HLA alleles (0, 1, or 2 copies of the shared epitope) demonstrated that parity decreased risk of severe RA in two outcomes, but only among women with no RA risk-associated HLA alleles. Among women with zero copies of the shared epitope, parous women had lower risk of severe erosion score (RR 0.28, 95% CI 0.09–0.89) and affected joint count (RR 0.28, 95% CI 0.09–0.87) compared to nulligravid women (Table 5).

4. Discussion

Some studies found parity to be protective against developing RA [7–11], whereas others did not [5,6,22]. One possible explanation for inconsistent findings is that effect of parity may decrease over time. A study based on 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 [10]. If risk factors for developing RA also contribute to RA progression, milder disease might be expected in parous than nulliparous women, and any protective effect of parity might be expected to decrease with latency.

The current analysis demonstrated no overall difference in risk of severe RA progression with respect to parity before RA onset. However, in the earlier study of risk in developing RA [10], parity distinctly differed from gravidity without parity and, in another study, miscarriages before RA onset were associated with increased joint damage [23]. Interestingly, in the current study, when women who had non-live birth pregnancies were

excluded, pre-onset parity was associated with decreased severity for one outcome measure, joint count. Among women who only had live birth pregnancies, stratifying by latency did not alter risk of severe RA.

A few studies have examined parity before RA onset and later severity with variable results; some suggested greater severity and others benefit [14–16,24]. Differing results may be contingent on numerous factors including gravidity without parity, latency, age, time from onset to severity measurement, and measure of severity (e.g., functional status, physical exam, radiographs, etc.). In a recent report that stratified by ACPA, parity was associated with RA severity evaluated by HAQ and DAS28 score in ACPA-negative women who were younger at onset [24].

Any immunological consequences of parity may play a secondary role to other factors in the progression of RA. Women who possess RA risk-associated HLA alleles are at higher risk for developing severe RA. In our study, only among women with zero copies of the RA risk-associated shared epitope did we observe a protective effect of parity on risk of severe RA measured by erosion score and joint count. That the relationship between pre-onset parity and RA severity is modified by the number of copies of the shared epitope may indicate that the effect of pre-onset parity is relatively small compared to the effect of a genetic predisposition to RA. As a result, the effect of parity on RA severity might only be observed in the absence of the RA risk-associated shared epitope. To fully address an association of parity with RA severity, knowing the child's HLA genotype would be important for assessing interactions with maternal HLA genotype. Some studies suggest increased RA risk if a woman's child's paternally-inherited HLA is RA risk-associated [25–27] but decreased risk if the non-inherited HLA from the patient's mother is associated with protection from RA [28,29].

The study has a number of limitations. The modest sample size and disease severity measurement at a single time point are limitations. If latency since birth is an important variable, our ability to address this was limited by the number of women with latency <15 years. Also, because of sample size constraints, we were unable to assess how specific types of disease-modifying drugs, intervening pregnancies, or adverse pregnancy outcomes might affect the relationship between parity and RA severity. Strengths of the current study include identification of women with newly diagnosed RA in a population-based cohort, detailed reproductive history, multiple objective outcome measures at long-term follow-up including hand and wrist radiographs, and high resolution HLA typing.

In summary, overall, we observed no significant difference in likelihood of severe RA by parity or latency. However, results suggest that additional pregnancies not resulting in a live birth may affect the direction and magnitude of risk for developing severe RA in relation to parity. Additional studies are needed to determine whether parity and/or gravidity affect RA prognosis but are modified by pregnancy outcome, with live births and short latency conferring some protection against severe RA and non-live births (stillbirths, pregnancy terminations, miscarriages/spontaneous abortions, ectopic pregnancies, etc.) possibly increasing RA severity. Here, parity was associated with lower risk of progression to severe RA as measured by erosion score and joint count for women without, but not with 1+ copies

of, the RA risk-associated HLA shared epitope sequence. Future research is also needed to clarify whether a child's HLA genotype might interact with the maternal HLA genotype to influence RA severity. Although reproductive history may influence a woman's risk of developing RA, the relationship of parity with long-term RA prognosis appears to be complex.

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Table 1:

Characteristics of women with RA at diagnosis by parity

	Number of Prior Deliveries (Parity)			
	1+ (n=156)		0 (n=66)	
Characteristic	**n**	**(%)**	**n**	**(%)**
Age (years)				
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)
Race/Ethnicity				
Non-Hispanic White	135	(86.5)	55	(83.3)
People of Color	21	(13.5)	11	(16.7)
# of Pregnancies (Gravidity)				
0			48	(72.7)
1+			18	(27.3)
Oral Contraceptive Use				
Never	45	(28.8)	20	(30.3)
Ever	110	(70.5)	46	(69.7)
Smoking Status				
Never	63	(40.4)	39	(59.1)
Ever	93	(59.6)	27	(40.9)

Table 2:

Serological and genetic features of RA and intervening characteristics between RA onset and study follow-up by parity

	Number of Prior Deliveries (Parity)			
	1+ (n=156)		0 (n=66)	
Characteristics	**n**	**(%)**	**n**	**(%)**
Rheumatoid Factor at Diagnosis				
Positive	81	(51.9)	35	(53.0)
Negative	75	(48.1)	31	(47.0)
ACPA at Diagnosis				
Positive	98	(62.8)	38	(57.6)
Negative	56	(35.9)	25	(37.9)
Missing	2	(1.3)	3	(4.5)
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)
Duration of Disease-Modifying Anti-Rheumati Drug (DMARD) Use *				
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)
DMARDs Ever Taken for ≥ 6 months				
None	39	(25.0)	14	(21.2)
Any DMARDs	114	(73.1)	49	(74.2)
Sulfsalazine	*26*	*(16.7)*	*13*	*(19.7)*
Oral Gold	*9*	*(5.8)*	*5*	*(7.6)*
Gold Shots	*31*	*(19.9)*	*10*	*(15.2)*
Methotrexate	*66*	*(42.3)*	*27*	*(40.9)*
Hydroxychloroquine	*52*	*(33.3)*	*31*	*(47.0)*
Chloroqulne	*4*	*(2.6)*	*3*	*(4.6)*
D-Penicillamine	*3*	*(1.9)*	*0*	*(0.0)*
Cyclophosphamide	*1*	*(0.6)*	*1*	*(1.5)*
Azathioprine	*5*	*(3.2)*	*1*	*(1.5)*
Etanercept	*1*	*(0.6)*	*0*	*(0.0)*
Cyclosporine	*0*	*(0.0)*	*0*	*(0.0)*
Leflunomide	*0*	*(0.0)*	*0*	*(0.0)*

	Number of Prior Deliveries (Parity)			
	1+ (n=156)		0 (n=66)	
Characteristics	**n**	**(%)**	**n**	**(%)**
Unknown	3	(1.9)	3	(4.6)

* During elapsed time from onset to follow-up

Table 3:

Risk of developing severe RA for women with prior deliveries relative to those without

	All Participants						Excluding Women with Non-Live Birth Pregnancies					
	Parous (n=156)		Nulliparous (n=66)		RR*	95% CI	Parous (n=86)		Nulligravid (n=40)		RR*	95% CI
Outcome	n	(%)	n	(%)			n	(%)	n	(%)		
Erosion Score	50/137	(36.5)	17/57	(29.8)	1.07	(0.65–1.78)	27/79	(34.1)	12/35	(34.3)	0.82	(0.47–1.44)
Joint Space Narrowing	62/137	(45.3)	18/57	(31.6)	1.67	(0.99–2.80)	37/79	(46.8)	12/35	(34.3)	1.41	(0.72–2.79)
Joint Count	50/156	(32.1)	21/66	(31.8)	0.74	(0.48–1.15)	25/86	(29.1)	15/40	(37.5)	0.55	(0.33–0.92)
HAQ Pain Score	62/144	(43.1)	19/63	(30.2)	1.24	(0.77–1.99)	27/78	(34.6)	9/39	(23.1)	1.12	(0.57–2.19)
HAQ Disability Score	74/146	(50.7)	21/63	(33.3)	1.38	(0.94–2.02)	33/79	(41.8)	12/39	(30.8)	1.22	(0.72–2.05)

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

Table 4:

Risk of developing severe RA for women with only live birth pregnancies relative to nulligravid women, stratified by latency

		Severe RA Outcome				
Outcome	**Latency**	**N**	**n**	**(%)**	**RR***	**95% CI**
Erosion	Nulligravid	35	11	(31.4)	1.00	ref
Score	< 15 years	18	3	(16.7)	0.69	(0.26–1.78)
	15+ years	61	20	(32.8)	1.01	(0.52–1.95)
Joint Space	Nulligravid	35	10	(28.6)	1.00	ref
Narrowing	< 15 years	18	2	(11.1)	0.49	(0.15–1.65)
	15+ years	61	25	(41.0)	1.54	(0.59–4.01)
Joint Count	Nulligravid	40	13	(32.5)	1.00	ref
	< 15 years	21	2	(9.5)	0.43	(0.11–1.72)
	15+ years	65	21	(32.3)	0.63	(0.36–1.lit
HAQ Pain	Nullgravid	39	13	(33.3)	1.00	ref
Score	< 15 years	19	7	(36.8)	0.99	(0.45–2.16)
	15+ years	59	28	(47.5)	1.10	(0.68–1.79)
HAQ	Nulligravid	39	12	(30.8)	1.00	ref
Disability	< 15 years	19	6	(31.6)	1.06	(0.49–2.29)
Score	15+years	60	27	(45.0)	1.24	(0.71–2.17)

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

Table 5:

Risk of developing severe RA for women with only live birth pregnancies relative to nulligravid women, by the number of copies of RA risk-associated HLA alleles

			Severe RA Outcome			
Outcome	**Copies of risk alleles**	**Parity**	**n**	**(%)**	**RR***	**95% CI**
Erosion	0	Nulligravid	3/10	(30.0)		
Score		Parous	6/26	(23.1)	0.28	(0.09–0.89)
	1	Nulligravid	6/18	(33.3)		
		Parous	14/39	(35.9)	0.97	(0.35–2.64)
	2	Nulligravid	3/7	(42.9)		
		Parous	7/14	(50.0)	2.14	(0.39–11.86)
Joint Space	0	Nulligravid	3/10	(30.0)		
Narrowing		Parous	13/26	(50.0)	1.20	(0.41–3.56)
	1	Nulligravid	6/18	(33.3)		
		Parous	19/39	(48.7)	1.66	(0.59–4.70)
	2	Nulligravid	3/7	(42.9)		
		Parous	5/14	(35.7)	0.65	(0.23–1.82)
Joint Count	0	Nulligravid	4/11	(36.4)		
		Parous	6/30	(20.0)	0.28	(0.09–0.87)
	1	Nulligravid	4/20	(20.0)		
		Parous	12/41	(29.3)	1.06	(0.41–2.78)
	2	Nulligravid	7/9	(77.8)		
		Parous	7/15	(46)	0.18	(0.03–1.14)
HAQ Pain	0	Nulligravid	4/11	(36.4)		
Score		Parous	9/26	(34.6)	0.53	(0.15–1.82)
	1	Nulligravid	3/20	(15.0)		
		Parous	12/39	(30.8)	1.22	(0.41–3.68)
	2	Nulligravid	2/8	(25.0)		
		Parous	6/13	(46.2)	1.50	(0.20–11.54)
HAQ	0	Nulligravid	4/11	(36.4)		
Disability		Parous	10/27	(37.0)	0.53	(0.20–1.40)
Score	1	Nulligravid	5/20	(25.0)		
		Parous	14/39	(35.9)	1.35	(0.52–3.53)
	2	Nulligravid	3/8	(37.5)		
		Parous	9/13	(69.2)	0.92	(0.45–1.85)

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