Genetic factors in human reproduction a trade off between procreation and longevity

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Miscarriage but not fecundity is associated with progression of joint destruction in rheumatoid arthritis

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ABSTRACT

Objective: To determine whether reproductive history prior to disease onset is associated with severity of joint destruction in rheumatoid arthritis (RA).

Methods: At the department of Rheumatology of the Leiden University Medical Center a special early arthritis clinic (EAC) was established. General practitioners were encouraged to refer patients with joint complaints to this clinic. Subsequently, the diagnosis RA was made by a rheumatologist. Of this cohort 113 female patients with definite RA were included in the current study. A structured questionnaire was taken and the joint damage was measured by sequential X-rays of hands and feet, using the modified Sharp score.

Results: The time of unprotected intercourse until first pregnancy (fecundity) was comparable with data of earlier studies, 16% of the RA patients reported a time to first pregnancy of more than 12 months. Fecundity did not reflect to the extent of joint damage over time. The miscarriage rate was 15% per pregnancy, comparable to population figures (12-15%). A significant increase in joint damage over a 2 year follow-up was found in RA patients who had experienced at least one miscarriage compared to patients who never had a miscarriage in the past (mean modified Sharp score at 2 years 24 (95% CI:15-32) and 16 (95% CI:10-23) respectively, $P<0.05$). At baseline the Sharp scores were similar in both subgroups.

Conclusion: Miscarriage prior to disease onset and not fecundity is associated with the progression of joint damage in RA patients.

INTRODUCTION

The balance between T helper-1 (Th-1) and T helper-2 (Th-2) production regulates various inflammatory responses in humans. Inborn differences in the Th-1/Th-2 balance may be present in Rheumatoid Arthritis (RA) patients with a more predominant Th1 activity(1). This Th1 phenotype is likely to exist form birth onwards and may protect against lethal infectious diseases all through life(2). A more profound Th2 activity is been suggested to be beneficial to the course of RA, as a lower amount of atopic disorders, known to be associated with Th2 predominance, was reported in RA patients(3). Furthermore, a reduced RA disease severity was found in patients whose atopy commenced before their RA development, suggesting an innate Th2 responsiveness(4). A Th2 immune response is likely to be of importance for a successful pregnancy(5). This predominant Th2 response could explain the ameliorating effect on established RA during pregnancy(6). Moreover, Th1 phenotype may result in aberrant characteristics in reproductive history before RA disease onset. This may be expressed in a decreased fertility (ability to become pregnant), fecundity (time to achieve pregnancy from the start of unprotected intercourse) and an increased miscarriage rate.

In 1965 Kay and Bach(7) reported a reduced fertility in pre-menopausal RA patients before and after the onset of RA. However, in a study reported in 1989, subfertility (not pregnant after two years of unprotected intercourse) did not occur more frequent in 117 RA patients compared to controls(8). Fertility in parous women does not seem reduced, as a smaller family size in RA patients has not been observed(9;10). Nulliparity has been reported to be associated to RA, with a consistent odds rate of around 2 for RA in nulliparous women compared to parous women(11). However, whether nulliparity is due to infertility, miscarriages or a choice to remain childless is not clear.

A decreased fecundity (time to achieve pregnancy from the start of unprotected intercourse > 12 months) prior to disease onset was reported in a study in 1993 of 259 RA patients compared to 1258 healthy controls(12). However, this was not confirmed in a study in 1999 where fecundity (> 12 months) in 167 RA patients was comparable to 105 neighbourhood

controls(13). Thus, the impact of RA on fertility and fecundity before disease onset has not been fully elucidated yet.

Miscarriage does not seem to occur more often in women who later develop RA compared to normal population controls(7;8;10;13-16). One American study however, did report a significantly higher number of miscarriages in RA patients but they were not compared to normal population controls but compared to patients with osteoarthritis and other musculosceletal conditions(17).

As many variations may effect human reproduction, as physiological, behavioral, demographic and environmental factors(18), a decreased fertility, fecundity and miscarriage rate in RA patients could also be due to inborn factors linked to RA, even before disease onset. A possible inborn Th1 phenotype may influence both reproductive and RA severity at different ages in life. Severity of RA has not been investigated so far in relation with reproductive success. The aim of the present study was therefore to investigate whether a less favorable reproductive outcome is associated with a more severe RA development. Thus, the reproductive history of women with newly diagnosed RA was studied in relation to the rate of joint destruction.

PATIENTS AND METHODS

Patients. In 1993, a special Early Arthritis Clinic (EAC) was started at the Department of Rheumatology of the Leiden University Medical Center, the only center for rheumatic patients in the rural area of Leiden and environs with 300,000 inhabitants. The general practitioners (GP's) were motivated to refer patients if at least two of the following features were present: joint pain, joint swelling and reduction of joint mobility. All patients referred to the special EAC by the GP's were seen within two weeks. The patients were included in the EAC if 1) arthritis was confirmed by a rheumatologist; 2) the history of symptoms lasted less than two years and 3) the patients had not been visiting a rheumatologist elsewhere for the same problem, to rule out second opinions. Subsequently, the diagnosis "definite RA" was made according to the 1987 ACR criteria(19) but without the requirement of a 6 weeks observation period of arthritis by a rheumatologist(20).

From 1993 to 1999, 644 consecutive patients were included in the EAC with a minimal follow-up of one year, of whom 379 were women. Of these 379 patients, 190 patients were excluded because they had did not have definite RA. Furthermore 8 patients had died (mean age 74 years old), 13 were lost to follow up (mean age 53 years old), 22 refused to participate after informed consent (mean age 67 years old), one patient was excluded because of language difficulties (51 years old) and 32 patients reported to have never had unprotected intercourse with the purpose to achieve a desired pregnancy (mean age 43 years old). This left 113 definite RA patients with a history of unprotected intercourse to be analyzed.

Reproductive history questionnaire. All 113 women were interviewed in respect to their reproductive history. The interview included questions concerning the number of pregnancies, the interval of unprotected intercourse until first pregnancy, number of pregnancy losses and the age during pregnancies. Time to pregnancy (fecundity) was defined as the self-reported time between child wish and unprotected intercourse and the occurrence of pregnancy. Fecundity was calculated for pregnancies that ended in the birth of a child as well as for pregnancies ending in miscarriage. Miscarriage was defined as the loss of a pregnancy prior to 20 weeks. The same person (DR), who was blinded for the diagnosis, interviewed all patients.

Assessment of outcome. The primary outcome was the radiographic joint damage, measured by the modified Sharp score(21). Radiographs of the hands and feet were taken at the time of diagnosis, at 6 months, at one year and at two year follow up. The radiographs were scored in random order by an experienced rheumatologist blind to the clinical data and not aware of the study questions. The intraclass correlation coefficient for the radiograph reading of the assessor was 0.95.

Secondary outcomes were a modified disease activity score(22) and the C-reactive protein (CRP) level at inclusion and during follow up. The disease activity score (DAS) was calculated as 0.53 * (Ritchie score)^{½} + 0.065 * (number of swollen joints) + 033 * ln erythrocyte sedimentation rate + 0.224. All joints were assessed as in the Ritchie Articular Index, except for the acromioclavicular, subtalar and midtarsal joints. For the swollen joint index the metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints were scored as one unit.

Statistical Analysis. The Statistical Package for Social Science (SPSS) was used for analysis of the results. The subgroups were tested using the Pearson's Chi-square test and Mann-Whitney U test, accordingly. Differences between the Sharp scores of the subgroups were tested with Mann-Whitney U test. All tests were 2-tailed and a P value less than 0.05 was considered significant.

RESULTS

Demographic and reproductive characteristics. One hundred and thirteen female patients with RA were included in this study. The general characteristics of all RA patients are shown in Table 1.

Table 1 Demographic and reproductive characteristics of the patients with rheumatoid arthritis at baseline.

	RA patients
Number of subjects	113
Ever pregnant (%)	110 (97)
Mean age at interview (SD)	59 (15)
Mean age at 1st visit (SD)	55 (15)
Mean duration of complaints at 1st visit in days (SD)	200 (160)
DMARD use (%)	99 (88)
Interval until start 1st DMARD in days (SD)	92 (144)
Rheumatoid factor positivity (%)	61 (54)
Pregnant before RA onset (%)	106 (94)

SD= standard deviation

DMARDs: disease modifying antirheumatic drugs

Fertility. Three patients (3%) had not achieved a desired pregnancy. They were 29, 30 and 37 years old at interview and had all been trying to conceive for more than a year. They had not had any fertility treatment yet.

Fecundity in relation to joint damage in RA. Of the 110 patients who had been pregnant at least once, 70 (62%) had reported that the time to their first pregnancy had been 3 months or less, 20 (18%) patients reported it had been 4 to 12 months and 18 (16%) patients reported it had been more than 12 months. Two patients could not recall the time it took to achieve their first pregnancy. When divided in groups according to their history of fecundity, the patient characteristics were similar in all subgroups (data not shown). Measuring the joint damage over time using the modified Sharp score (0, 6, 12 and 24 months), there was no difference in the development of joint destruction in these three fecundity groups (Table 2). When the patient group with a fecundity ≤ 12 months was compared to the patient group with a fecundity >12 months, the mean Sharp score was comparable (at baseline: mean Sharp score 4 (95% confidence interval [CI]:2-7) and 8 (95% CI:-5-21), respectively and at two years: mean Sharp score 17 (95% CI:12-23) and 25 (95% CI:7-43), respectively).

Table 2 Mean Sharp scores for 110 patients with rheumatoid arthritis according to fecundity

	Sharp at baseline	Sharp at 6 months	Sharp at 12 months	Sharp at 24 months
Fecundity				
< 3 months (n=70)	5.0 (1.3)	9.7 (2.2)	15.7 (2.7)	19.3 (3.3)
4 – 12 months (n=20)	2.2 (0.9)	3.8 (1.3)	5.4 (1.3)	11.9 (3.2)
> 12 months (n=18)	8.3 (6.1)	10.1 (5.3)	21.3 (10.2)	25.0 (8.2)

Miscarriage in relation to disease severity in RA: Joint damage. The miscarriage rate per pregnancy was 15% for the 110 RA patients with at least one pregnancy in the past. The patient characteristics were comparable when these patients were divided according to their miscarriage history (Table 3). The patient group with at least one miscarriage understandably

experienced significantly more pregnancies to achieve a similar mean amount of children (Table 3).

Table 3 Demographic and reproductive characteristics of patients with rheumatoid arthritis with at least one pregnancy (n = 110) at baseline, divided by history of miscarriages.

	0 Miscarriages (n = 74)	≥ 1 Miscarriages (n = 36)
Mean age at interview (SD)	59 (14)	62 (15)
Mean age at 1st visit (SD)	55 (14)	58 (15)
Mean duration of complaints at 1st visit in days (SD)	186 (149)	236 (181)
DMARD use (%)	63 (85)	33 (92)
Interval until start 1st DMARD in days (SD)	84 (107)	109,3 (203)
Rheumatoid factor positivity (%)	38 (55)	23 (66)
Pregnant before RA onset (%)	72 (97)	34 (94)
Mean age at 1st pregnancy (SD)	26 (5)	27 (5)
Mean number of pregnancies (SD)	2,3 (1.1)	4,1* (1.9)
Mean number of children (SD)	2,3 (1.1)	2,8 (1.9)
Marital status, currently married (%)	59 (80)	26 (72)
Ever smoked (%)	20 (27)	6 (17)
Education: college or university (%)	18 (24)	9 (25)

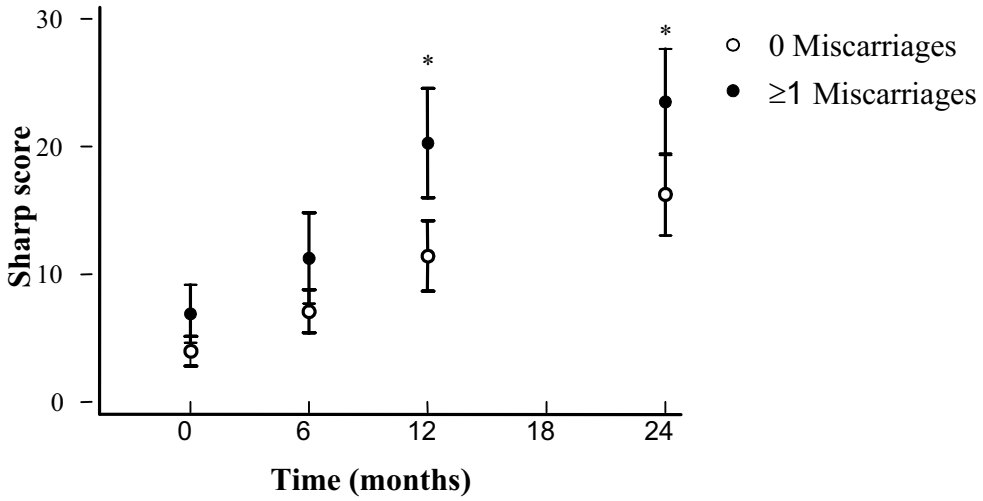
SD= standard deviation, DMARDs = disease modifying antirheumatic drugs

* P<0,05, compared to the group without miscarriages.

The modified Sharp score over a two-year period was analyzed (0, 6, 12 and 24 months) for each of the subgroups. A significant increase in joint destruction was found in women who had experienced at least one miscarriage in the past compared to women who did not have any miscarriages in the past (Figure 1). At inclusion the mean Sharp score was 4 (95% CI: 1-

7) for the group without miscarriages and 7 (95% CI: 2-11) for the group with at least 1 miscarriage. The group without miscarriages progressed to a mean Sharp score of 16 (95% CI: 10-23) after two years follow-up, while the group with at least one miscarriage progressed to a mean Sharp score of 24 (95% CI: 15-32; $P<0.05$ compared with the group without miscarriages). The outcome was similar when patients were excluded who had their first pregnancy after the onset of the disease (n=4). A multivariate analysis was preformed for prognostic factors as age at onset, duration of complaints before referral, rheumatoid factor and shared epitope, this did not alter the outcome significantly.

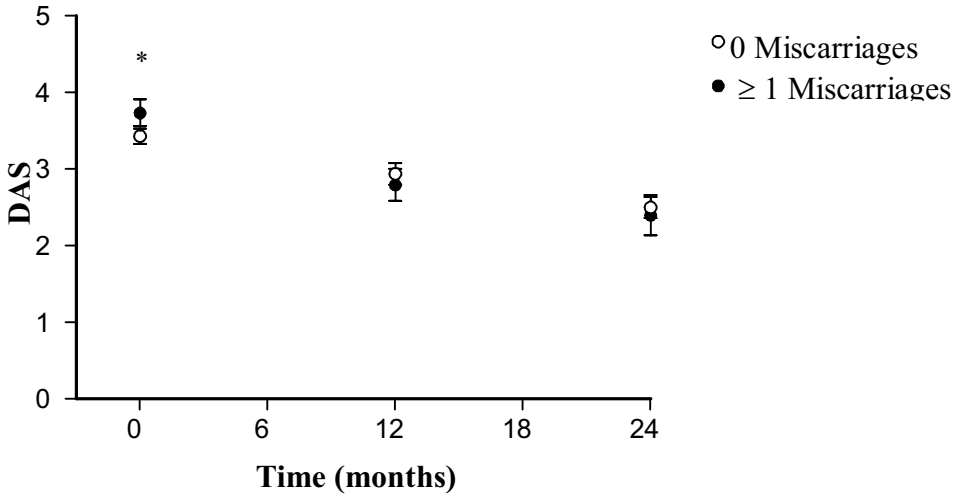
Figure 1 Mean Sharp scores over time as a measure of joint damage in patients with rheumatoid arthritis according to their history of miscarriages (*p<0.05 for the two subgroups). Error bars = SEM.



Miscarriage in relation to disease severity in RA: Activity outcome of disease. The mean DAS at baseline was 3.4 (95% CI: 3.2-3.6) for the group without miscarriages and 3.7 (95% CI: 3.4-4.1; $P=0.05$) for the group with at least one miscarriage (Figure 2). The DAS improved in both groups and were comparable for the two subgroups for the duration of the follow-up period of 2 years (2.5, 95% CI: 2.2-2.8 and 2.4, 95% CI: 1.9-2.9, respectively at 2 years). At baseline the mean CRP level (Figure 3) was significantly lower in the group without miscarriages (24, 95% CI: 17-30) compared to the group with at least one miscarriage

(41, 95% CI: 27-55, *P*<0.05). During the two years follow up the CRP levels were similar in both groups (15, 95% CI: 8-22 and 18, 95% CI: 5-31, respectively).

Figure 2. Mean (standard error) disease activity scores during follow up in RA patients according to their history of miscarriages (* P< 0.05 for the two subgroups).



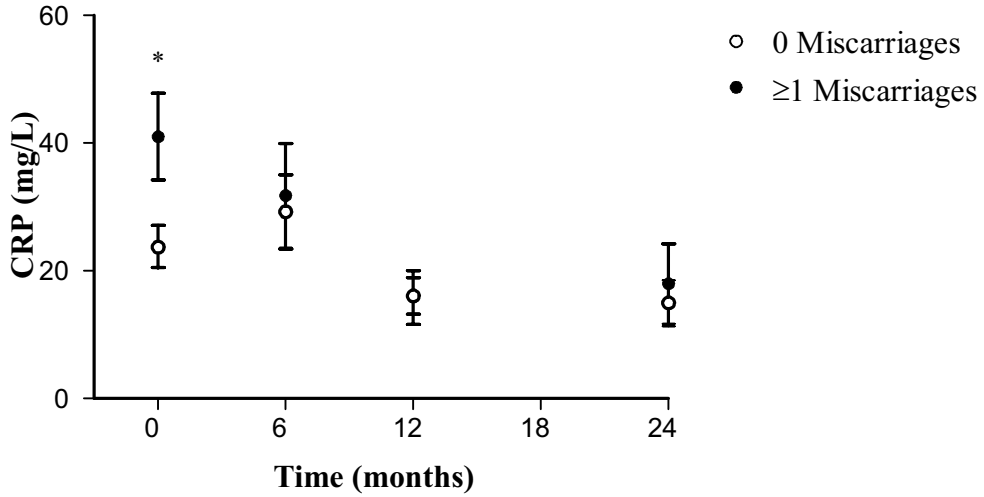
DISCUSSION

In this study, we observed that a high rate of joint damage in RA patients is associated with a history of miscarriage but not with history of a prolonged fecundity. To our knowledge this is the first study in which the severity in disease course of RA patients, as measured by rate of joint destruction, is related to reproductive history.

The miscarriage rate per pregnancy in our study was 15%, which is consistent with the miscarriage rate of 12-15% in the normal population(23). In the literature the miscarriage rate has been reported to be comparable between RA patients and healthy population control groups(7;8;10;13-16). However, we did find a relationship between miscarriage and severity of RA. The history of at least one miscarriage increased the rate of joint damage in RA patients by 2-fold over a 2 year follow-up period. Two years is a relatively short time to assess outcome and a longer follow up would have been preferable, although radiological

damage is known to occur early in RA. The association between miscarriage and severity of joint damage in RA could not be explained by a significant difference in the duration of complaints before inclusion, or by a difference in treatment strategy between the two groups. At baseline the group with at least one miscarriage had a significantly higher CRP level and a significantly higher DAS relative to the group without a miscarriage, indicating that this subgroup had more severe symptoms at first visit. At follow-up however, both CRP and DAS decreased to similar levels in both subgroups, indicating that the RA symptoms were treated sufficiently in both subgroups. The radiographic joint damage using the modified Sharp score was the only measure that was similar at baseline and progressed significantly in the group with at least one miscarriage at 1 and 2 years follow-up, compared to the group without miscarriages. A history of miscarriage may represent a group with a more severe disease activity, which will lead to a higher progression in joint damage, possibly reflecting the Th1 phenotype in this subgroup.

Figure 3 Mean C reactive protein concentrations during follow up in the patients with rheumatoid arthritis according to their history of miscarriages (*p<0.05 for the two subgroups). Error bars = SEM.



This cytokine mechanism could explain the difference in progressive joint damage in the two subgroups. An inborn predominant Th-1 response in the miscarriage subgroup may be harmful to both the disease process in the joint and to the physiological immunological

changes during pregnancy, even before clinical disease manifestation. A predominant Th2 response is necessary for normal pregnancy, this predominance is less clear in pregnancies undergoing spontaneous abortion(24). The probability of normal fecundity increased more than tenfold when the innate cytokine profile was characterized by a Th2 responsiveness, compared to the profile of women with recurrent abortion, whose cytokine profile was characterized by low Th2 and high Th1 responsiveness(25). A more pronounced inborn Th-1 profile may characterize women who experience miscarriage and if these women develop RA, it is conceivable that their RA is characterized by more extensive joint destruction.

A decreased fertility rate is difficult to assess, as the ability to have a child is dependent on numerous factors both related to male and female factors. In our study 16% of the RA patients reported a time to pregnancy of more than 12 months. Fecundity in the normal population is reported to be 58-65% for the first 3 months, 85-90% for the first 12 months and the remaining 10-15% have a time to pregnancy of more than a year(26;27). Decreased fecundity (prolonged interval until desired pregnancy) in RA patients seems plausible(12;28). The 16% reported in our study is comparable, however, a population control group was not available. A probable decreased fecundity rate in RA may represent the effect of an inborn characteristic in these RA patients. However, a relation to disease severity and joint damage could not be revealed in this study, possibly due to the small numbers in this subgroup.

In the current retrospective study, reproductive data were collected through interview. Time to pregnancy measured in months is known to be a sensitive measure of the biological fertility of a couple(26). Recall bias is possible, however, validation studies of fecundity and miscarriages have shown a good match between long-term recall (>15 years) of personal reproductive history collected either through personal interview, telephone interview or written questionnaire compared to medical data(29;30). Even though our group consisted of a different patient group at a different time period, we presumed that these validation studies are applicable on our study.

In summary, the current study indicates that miscarriages prior to disease onset in RA patients is comparable to what is reported in the normal population, but after developing RA, a history of miscarriage may lead to a higher rate of joint destruction. Fecundity seems to be decreased in RA patients prior to disease onset, however this study failed to reveal a relation to joint

damage, possibly due to small numbers. The results could indicate that the phenotype of joint destruction is associated with the phenotype of reported miscarriages, suggesting common genetic risk factors for each of these two traits, possibly through the innate Th-1/Th-2 phenotype.

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