Adverse reproductive outcomes in women who subsequently develop rheumatoid arthritis

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SUMMARY The rates of adverse reproductive outcomes in 40 women with rheumatoid arthritis (RA) were compared with 67 of their unaffected female relatives. All women were aged between 35 and 65 years at the time of inquiry. Seven of the women with RA reported a perinatal death (six stillbirths, one early neonatal death) compared with one woman in the unaffected group: estimated age adjusted relative risk (R)=12.4, 95% confidence interval (95% CI) 1.6–91.1. The rate of spontaneous abortions was, however, not significantly different between the two groups (R=1.2, 95% CI 0.5–2.9). All the perinatal deaths occurred before clinical disease onset in the women with RA. It is possible that in these two groups of women with a similar genetic background perinatal loss may be related, at least in part, to disease expression.

Key words: fetal wastage, familial studies.

Recent reports suggest that adverse outcomes of pregnancy may predate the diagnosis of autoimmune disease, especially among women who later develop thyroid disease and diabetes.^{1,2} There is an association between rheumatoid arthritis (RA) and autoimmune thyroid disease both in individuals and in families³; and it is thus of interest that women with RA may have a higher rate of fetal loss before the clinical onset of their disease.⁴ A recent review of the epidemiological data on RA and its relation to hormones and pregnancy also concluded that the available data were consistent with an association between fetal loss and subsequent development of this disease.⁵ We investigate here the hypothesis that the prior occurrence of fetal loss was greater in women with RA than that of their disease free, female relatives.

Subjects and methods

The subjects were recruited from The London Hospital study of multicase rheumatoid arthritis families,⁶ in which all first degree relatives of probands with RA were interviewed, examined, and blood taken for immunogenetic and serological

analysis. All subjects were then classified into one of three groups based on American Rheumatism Association criteria⁷: unaffected, probable, and definite/classical RA. The date of disease onset in the women with RA was taken as their recalled year of first symptoms. For this investigation all women examined in the study between 1983 and 1985, who were aged 35–65 years of age at the time of examination, were included. Within this restricted age band it was hoped that the women were more likely to have completed their families and yet still recall their reproductive history reliably. Information about the women's reproductive history was obtained using a reply paid postal questionnaire, which was issued either at examination or sent subsequently. The information requested included date of birth, marital status, and date and outcome of each pregnancy. The questionnaire was previously tested in 12 outpatient attenders by comparing their replies with those given in a probed clinical interview. There were no disagreements.

Of the 128 questionnaires distributed, 111 (87%) were returned completed. Four women were excluded from the analysis because clinical data were insufficient to classify their disease status. Of the remaining 107 women, 40 had rheumatoid arthritis and 67 were disease free.

The characteristics of the two groups were compared as was their history of specific reproductive

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Table 1 Comparison of the characteristics and reproductive history of women with rheumatoid arthritis and their unaffected female relatives

	Women with RA (n=40)	Female relatives without RA (n=67)
Ever married (No,%)	37, 93	62, 93
Nulliparous (No, %)	1, 3	3, 4
Mean age at interview (SD)	50.6 (7.6)	44.8 (7.0)
Mean age at first pregnancy (SD)	22.6 (2.9)	23.2 (4.4)
Pregnancies		
Total number	113	182
Mean per parous women	3.1	3.1
Perinatal death (No, % of pregnancies)	7, 6	1, 0.5
Spontaneous abortion (No, % of pregnancies)	12, 11	15, 8

outcomes. Relative risk (R) estimates and 95% confidence intervals (95% CI) were calculated, adjusting for age at the time of interview, using standard Mantel-Haenszel procedures.⁸

Results

Table 1 shows the results of the study. The two groups were similar with regard to marital status, the proportion nulliparous, the mean number of pregnancies per women, and average age at first pregnancy. At the time the survey was carried out women with RA were, on average, 5.8 years older than their unaffected female relatives ($p<0.01$). Seven perinatal deaths (six stillbirths and one early neonatal death) were reported by the women with RA. These seven events occurred to seven different women before their first reported symptoms of disease. By contrast, only one perinatal death (a stillbirth) was reported by the unaffected group. After adjustment for age at interview this difference in event rate yielded an estimated relative risk of 12.5, which was significantly increased at the 5% level (95% CI 1.6–91.1). The rate of spontaneous abortions was, however, similar ($R=1.2$, 95% CI 0.5–2.9).

Discussion

The women with RA reported significantly more perinatal deaths than their unaffected female relatives. Although 12 (30%) of the 40 women with RA recalled first symptoms at ages below 35 years, all the perinatal losses described above occurred before the onset of disease. The findings described here for

rheumatoid arthritis are similar to those described for women with 'autoimmune diabetes': women with insulin dependent diabetes who subsequently developed thyroid disease or pernicious anaemia reported more perinatal deaths than other insulin dependent diabetics, even before their diabetes was diagnosed.^{1,2}

The findings in the present study should be interpreted with caution as the numbers are small and the confidence intervals wide. A larger study would be necessary to define more accurately the magnitude of the increased risk. There is also the potential bias that the women with RA might have been more likely to recall perinatal loss than their unaffected relatives. This seems unlikely as perinatal death is a major life event which women would be expected to recall without difficulty.

The comparison group in this study were unaffected female relatives of the patients with RA and were not typical of the general population. It is of interest, therefore, to compare the perinatal loss rates observed in this study with those of the general population. The England and Wales perinatal mortality rates for the years 1962 and 1966 were 30.8 and 23.3 per 1000 respectively.⁹ These years correspond to the average years the women had their pregnancies and can be compared with the observed rates of 72.9 and 6.2 per 1000 for the cases and comparison groups respectively. Thus the rate in the cases was still considerably in excess of national rates, whereas the comparison group had a much lower rate than the national rate. The case and comparison groups were, however, similar with respect to factors such as age at first pregnancy, gravidity, and marital status (see Table 1). Also, as these women came from the same families they were presumably of similar genetic, social, and educational background. The effect of this similarity would be to minimise the expected difference in perinatal mortality—that is, against the direction of the hypothesis under test.

We were unable reliably to determine the cause of the stillbirths reported and hence to separate out those, if any, with a mechanical cause. If stillbirths were biologically related to RA it might be expected that the excess number in our case group was due to factors such as premature rupture of membranes and intrauterine growth retardation.

No significant excess of spontaneous abortion was reported by the women with RA in the present study. This contrasts with a recent observation suggesting an excess of 50% over a comparison group of women with osteoarthritis.³ An earlier study, however, failed to show such an increase: 13.5% of all pregnancies against 11.2% in general practitioner controls.¹⁰

The affected and unaffected women were similar genetically. Thus many of the unaffected women in the present study were HLA identical with or carried the same DR4 haplotype as their affected relatives,⁶ and thus other factors must be sought to explain differences in disease expression. One possible factor in these families is the occurrence of an adverse obstetric event such as perinatal loss. Alternatively, the women with RA may already have had a subclinical immunological abnormality, which increased their risk of perinatal loss, without displaying itself as clinical disease until many years later. It is impossible to distinguish between these two explanations with the available data.

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