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Is poor pregnancy outcome a risk factor in rheumatoid arthritis?

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Abstract

Previous work has suggested that prior poor reproductive outcome may be a risk factor in rheumatoid arthritis (RA). A case-control study of 195 women with RA and 462 control women from two different sources is presented here. No increase in rates of spontaneous abortion was seen in the women with RA; indeed a protective effect was seen with an age adjusted odds ratio of 0·6 (95% confidence interval (CI) 0·4 to 0·9). A non-significant increase in stillbirth rates was seen in women with RA, producing an age adjusted odds ratio of 1·5 (95% CI 0·7 to 3·4). No differences in rates of induced abortion were seen. Thus although hormonal and gynaecological factors are undoubtedly important in the aetiology of RA, it was not possible to confirm that prior poor reproductive outcome is a risk factor in RA.

Rheumatoid arthritis (RA) is a disease of unknown aetiology, characterised by a 3:1 female to male sex ratio.[1] The disease commonly remits during pregnancy and relapses after delivery[2] and alters during the menstrual cycle.[3] Pregnancy itself may be a risk factor for RA,[4] though population based epidemiological studies have produced conflicting results.[5] An extension of this hypothesis is that poor reproductive outcome is a predictor of future risk.[6] A small case-control study comparing women with RA with their unaffected female relatives showed an increased rate of stillbirth before disease onset in the former,[7] whereas a study of a mainly urban black population in the United States showed an increase in spontaneous abortion.[8] We therefore undertook a case-control study of obstetric factors in women with RA using two different comparison groups to explore further whether poor reproductive outcome before the development of RA was a risk factor for the disease.

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Patients and methods

The patients comprised women aged 35-70 with definite RA (1958 American Rheumatism Association criteria) currently attending one of six rheumatology centres in East London. The controls who were within the same age range were (*a*) women with a clinical diagnosis of osteoarthritis (OA) attending the same clinics; (*b*) women randomly selected from electoral registers in Greater London.

Information on obstetric and gynaecological history was obtained by means of a postal questionnaire which had been validated with interview as part of a previous study[7] and with obstetric records by other authors.[9] Details were obtained of year of birth, marital status, menarche, menopause, spontaneous and induced abortions, dates and outcomes of each pregnancy, and for the hospital (arthritis) groups, age of disease onset. For the hospital groups the diagnosis and dates of disease onset were validated wherever possible with the clinical records by the authors.

After a second reminder letter usable replies were received from 260 women with RA with a response rate of 89%, 292 women with OA (85%), and 267 women from the electoral register (71% approx). (The numbers of non-responders in the age range could not be calculated exactly, and this figure is an estimate.) This analysis was restricted to those women reporting at least one pregnancy. Further, as the aim was to investigate reproductive loss before disease onset, women in the RA and OA groups whose reported disease onset was before their last pregnancy were also excluded (n=22). This left 195 women with RA, 233 with OA, and 229 population controls for further analysis. As an additional comparison group, replies were used from a similar questionnaire which had been sent to 708 women aged 35 to 65 from a local general practice as part of another study. The response rate from this group was 72% (508 women).

ANALYSIS

The rates of reproductive loss were expressed both as a percentage of the total number of pregnancies and as the percentage of women experiencing at least one poor reproductive event. Crude odds ratios and the 95% confidence intervals were calculated for stillbirths and spontaneous and induced abortions. Differences in age were accounted for by using the stratified analysis method of Mantel-Haenszel.

Results

Table 1 gives the baseline characteristics for the four groups. The mean age in the groups ranged from 52 to 58 years, the population control groups being approximately five years younger than the arthritis groups. The mean ages of first symptoms were 46·4 (SD 9·9) and 46·2 (11·2) years and of first referral 48·6 (10·1) and 51·3 (9·7) years for the RA and OA groups respectively.

The effect of pregnancy outcome was studied for each individual. In the three groups 1840 pregnancies were available for analysis (table

Table 1: Baseline characteristics

Characteristic	*RA* (n=195)*	*OA* (n=233)*	*ER* (n=229)*
Mean age (SD)	57·7 (7·6)	57·2 (9·0)	52·7 (10·2)
Number unmarried (%)	3 (2)	8 (3)	13 (6)
Mean age first symptoms (SD)	46·4 (9·9)	46·2 (11·2)	—
Mean age first referral (SD)	48·6 (10·1)	51·3 (9·7)	—

*RA=rheumatoid arthritis; OA=osteoarthritis; ER=electoral register.

2). Pregnancies ending as ectopic pregnancies were treated as spontaneous abortions for the analysis. Subgroup analysis by birth order and maternal age did not explain any differences in pregnancy outcome between the three groups of women, and the analysis presented is therefore based on all pregnancies regardless of maternal age or birth order.

The number of live births per woman was similar in the three groups (range 2·3 to 2·4). No increase in spontaneous or induced abortions or postnatal deaths was noted in the RA group compared with the controls. Indeed the women with RA had lower rates of spontaneous abortions than the other groups, implying a protective effect with an age adjusted odds ratio for RA *v* all controls of 0·6 (95% CI 0·4 to 0·9). There was a slightly higher rate of stillbirths among the women with RA, but this failed to reach statistical significance. (Age adjusted odds ratio for RA *v* all controls of 1·5 (95% CI 0·7 to 3·4).) Table 3 gives in full the crude and age adjusted odds ratios for RA *v* control groups.

Further strengthening of these findings comes from the extra comparison group from the local general practice. Of the 508 women who replied, 1053 pregnancies were reported. Of these women, 112 (26·5%) had experienced at least one spontaneous abortion and 16 (3·8%) reported a stillbirth. These rates corresponded closely with those from the other comparison groups, and inclusion of these figures did not alter the conclusions. The rate of multiple birth was similar in the three groups: eight twin pairs in RA (4·1% of women), 10 in OA (4·3%), and eight in the population (3·5%), and no differences were found in birth weights or sex ratios of children.

Discussion

These data do not support our earlier hypothesis that women with RA have an increased rate of spontaneous abortions or stillbirths before the onset of the disease. The figures for miscarriages in the control groups fall within the recalled figures for pregnancies ending in clinical miscarriage in the United Kingdom,[10] and thus appear representative of the population. The similarity in rates between the population control groups also supports this. The rates for stillbirth were marginally higher in the RA group, though not significantly so. This study was of sufficient size to have an 80% power to detect a doubling in stillbirth rate. Women's recall of pregnancies and miscarriages has been found to be accurate,[9] though small differences between responders and non-responders have been found in some studies,[11] while others have found no differences.[12]

So although the possibility of a small effect of stillbirth cannot be excluded, as the rate of stillbirth in the population is low the number of

Table 2: Reproductive outcomes

	*RA** (n=195)	OA* (n=233)	ER* (n=229)
Total pregnancies	519	679	642
Outcomes			
Live births (alive at 12 months) (mean number/woman)	457 (2·3)	545 (2·3)	547 (2·4)
Spontaneous abortions			
Number (% of total pregnancies)	34 (6·5)	95 (14·0)	59 (9·2)
Number of women (%)	28 (14·3)	64 (27·5)	44 (19·2)
Induced abortions			
Number (% of total pregnancies)	15 (2·9)	19 (2·8)	16 (2·5)
Number of women (%)	13 (6·7)	12 (5·1)	14 (6·1)
Stillbirths			
Number (% total livebirths)	10 (2·2)	10 (1·8)	7 (1·3)
Number of women (%)	9 (4·6)	10 (4·3)	7 (3·0)
Infant deaths			
Number (% of total pregnancies)	3 (0·6)	10 (1·5)	13 (2·0)
Number of women (%)	3 (1·5)	7 (3·0)	12 (5·2)

*RA=rheumatoid arthritis; OA=osteoarthritis; ER=electoral register.

Table 3: Relative risks: crude and age adjusted odds ratio

	RA v* OA*	RA *v* ER*	RA *v* Both
Stillbirths			
Crude OR* (95% CI*)	1·1 (0·4 to 2·7)	1·4 (0·4 to 4·6)	1·5 (0·7 to 3·4)
Rmh* (95% CI)	1·0 (0·4 to 2·6)	1·8 (0·5 to 6·9)	1·5 (0·7 to 3·4)
Spontaneous abortions			
Crude OR (95% CI)	0·4 (0·3 to 0·7)	0·7 (0·4 to 1·2)	0·55 (0·3 to 0·7)
Rmh (95% CI)	0·4 (0·3 to 0·7)	0·9 (0·5 to 1·6)	0·6 (0·4 to 0·9)
Induced abortions			
Crude OR (95% CI)	1·3 (0·6 to 2·9)	1·1 (0·5 to 2·4)	1·2 (0·6 to 2·4)
Rmh (95% CI)	1·4 (0·6 to 3·0)	2·7 (1·0 to 7·1)	1·7 (0·8 to 3·4)

*RA=rheumatoid arthritis; OA=osteoarthritis; ER=electoral register; OR=odds ratio; CI=confidence interval; Rmh=Mantel-Haenszel adjusted odds ratio.

cases of RA being attributable to stillbirths will be small (estimated population attributable risk is 2·2%).

Studies on the effect of reproductive outcome have previously been performed. The study of Kay and Bach of 209 women with RA looked at miscarriage rates and found no differences compared with general practice controls.[13] A study by Kaplan of 96 women with RA found a 50% increase in rates of miscarriage but not induced abortions compared with 113 controls with OA.[8] The discrepancies of this study and our own are difficult to explain, but the most striking difference between the study populations was the racial characteristics—in Kaplan's study only 16% of the women were white. Although in our study the women were not systematically categorised into racial groups, an estimated 95% were white, suggesting that the results of the former study may not be easily extrapolated to white populations. The other point is that our study was considerably larger, having an 80% power to detect an odds ratio of 1·5 for miscarriage rates.

The results from this study for stillbirths are at variance with our recently reported observations, using the same methodology, showing a markedly increased perinatal loss in women with RA.[7] The patients in that study were a small group of women with RA from multicase families, who were compared with their unaffected female relatives. As stated in that report the latter group had an unusually and inexplicably low rate of perinatal loss. Nevertheless, it is possible that late reproductive loss is only of importance in those particularly genetically susceptible to RA.

Although sex hormones and pregnancy undoubtedly play a part in the aetiology and pathogenesis of RA, we were unable to confirm the findings of previous studies of increased poor reproductive outcome before disease onset in women with RA. Indeed the results of this study suggest that spontaneous abortions may actually have a 'protective effect' on the development of RA, though further studies are needed before any firm conclusions are reached.

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