

## EXTENDED REPORT

# Multiple adverse pregnancy outcomes before symptom onset are associated with a worse disease outcome in women with recent-onset inflammatory polyarthritis

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**ABSTRACT**

**Objective** Previous evidence suggests that women with a history of adverse pregnancy outcomes (APOs) may be at greater risk of developing rheumatoid arthritis. Additionally, one study reported that female patients with rheumatoid arthritis with a history of preonset APOs showed a worse 2-year radiographic outcome than did patients with no APOs. The authors' aim was to investigate the relationship between preonset APOs (spontaneous abortion or stillbirth) and disease outcome in women with inflammatory polyarthritis (IP).

**Methods** The Norfolk Arthritis Register (NOAR) is a primary-care-based cohort of patients with recent-onset IP; 1586 gravid women who joined NOAR during 1990–2004 were included in this analysis. The authors examined the relationship between patient-reported preonset APOs and disease outcome, measured using the Health Assessment Questionnaire (HAQ) and disease activity score in 28 joints (DAS28<sub>CRP</sub>) (for a subgroup of patients), using linear random effects analysis, adjusted for age and other factors.

**Results** In a predominantly parous cohort (99%), 397 (25%) women reported  $\geq 1$  APO before symptom onset. The rates of APOs in NOAR were comparable to the general population. On average, women with a history of  $\geq 2$  APOs had significantly higher HAQ and DAS28 scores over time than women with no APOs (mean difference in HAQ 0.13 (95% CI 0.002 to 0.26); DAS28, 0.56 (95% CI 0.01 to 1.11)). This relationship was more pronounced in women with  $\geq 3$  APOs (mean difference in HAQ 0.23 (95% CI 0.02 to 0.43); DAS28, 0.98 (95% CI 0.23 to 1.74)).

**Conclusion** Women with two or more APOs before IP onset had a worse disease outcome than women with no APOs.

These studies included a range of 'adverse pregnancy outcomes' (APOs), namely, SA, stillbirth, induced abortion (IA), premature birth and ectopic pregnancy. Some studies reported a statistically significant positive association between APOs before symptom onset and subsequent development of RA,<sup>1 3 8</sup> whereas others reported a significant negative association.<sup>1 5</sup> However, most found no significant association,<sup>2 4 6 7</sup> although the sample sizes were small in many of these investigations. However, a large national cohort study in Denmark, which included 23.5 million person-years of follow-up, also reported a comparable risk of RA whether or not women had a history of SA or stillbirth.<sup>9</sup>

The relationship between APOs and subsequent disease outcome in RA has been less studied. In a prospective study from the Netherlands, the relationship between preonset SA (0 vs  $\geq 1$ ) and radiological progression was examined in 110 gravid patients with early arthritis.<sup>10</sup> The 36 (33%) women who had one or more (1+) SA before symptom onset showed a statistically significantly faster rate of radiographic joint damage over 2 years of follow-up than women with no SAs before symptom onset.

The finding from this small study requires replication in a larger cohort of patients. Our aim was to compare disease outcome, in terms of physical function and disease activity, in gravid women with recent-onset inflammatory polyarthritis (IP) who did and did not have a history of APOs prior to symptom onset.

**PATIENTS AND METHODS****Setting**

The Norfolk Arthritis Register (NOAR) is a large primary-care-based inception cohort of patients with recent-onset IP, presenting to a physician with  $\geq 2$  swollen joints, persisting for  $\geq 4$  weeks. A detailed description of the register has been published elsewhere.<sup>11</sup>

**Patients**

The cohort initially included in the current investigation comprised 1647 consecutive women registered with NOAR between January 1990 and December 2004, who reported ever being pregnant (gravid) before IP symptom onset. For the purposes

**INTRODUCTION**

In 1986, a case-control study from the USA reported that prior to symptom onset, women with rheumatoid arthritis (RA) (n=89) had a higher spontaneous abortion (SA):live birth ratio than controls without RA (n=113).<sup>1</sup> Subsequently, a number of case-control studies that attempted to replicate this finding were conducted in Europe and the USA. Their results, and those from one earlier study, are summarised in table 1.<sup>1–8</sup>



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of this analysis, patients were followed until either their 10th anniversary assessment or February 2009 (whichever came first). Forty-six women who became pregnant during follow-up were excluded from this analysis.

### Adverse pregnancy outcomes

Patients were asked to report the calendar year and outcome (live birth, stillbirth, SA or IA) of all past pregnancies. Throughout this analysis, 'parous' denotes women who reported having at least one live birth, and an APO was defined as either a stillbirth or an SA. Pregnancies resulting in an IA were not included in this analysis. Thus, 12 women who reported only pregnancies that resulted in a termination were excluded from this analysis. The remaining patients were first classified as either having no history of APOs or having at least one (1+) APO. This subgroup was then further stratified into those who had two or more (2+) APOs and, subsequently, into those who had three or more (3+) APOs.

### Data collection

Baseline assessment was carried out by a research nurse who recorded demographic details, date of symptom onset and medical history. A tender and swollen joint examination was performed and blood samples were taken, from which serum was later tested for rheumatoid factor (RF) (latex method; positive: titre  $\geq 1:40$ ) and C reactive protein (mg/l—endpoint immunoturbidimetric agglutination method). The swollen and tender joint counts and C reactive protein concentration were used to calculate a baseline disease activity score in 28 joints (DAS28).<sup>12</sup> Patients also completed the British version of the Stanford Health Assessment Questionnaire (HAQ),<sup>13</sup> which is scored between 0 and 3, with 3 indicating the greatest degree of functional disability. Patients reported whether they were past smokers or current smokers or if they never smoked. Follow-up assessments were performed by a research nurse at 1–3, 5, 7 and 10 years after the baseline assessment. At each assessment, the patient completed the HAQ and was asked to report any comorbid diseases and any medication (including the contraceptive pill (CP)) that she had taken since her last assessment. The 1987 American College of Rheumatology (ACR) classification criteria for RA<sup>14</sup> were applied cumulatively at each anniversary. The DAS28 score was calculated again at the 5th and 10th anniversaries only, when further blood samples were collected.

Socioeconomic status was defined by patient's occupation or, if unavailable, by spouse's occupation where possible (I/II: professional or managerial, III-NM: non-manual skilled, III-M: manual skilled, IV/V: partly skilled or unskilled).

### Statistical analysis

All analyses were carried out using the Stata V.10 software package. Differences in baseline characteristics by APO history were tested using Mann–Whitney and  $\chi^2$  tests, as appropriate to the data characteristics. Linear random effects (LRE) models are a statistical technique used to analyse longitudinal, repeated-measures data.<sup>15</sup> LRE models simultaneously account for variation between individuals and within each individual's repeated measurements over time. With sufficient data points, patients with different numbers of outcome measurements can be included in the same model, thus minimizing the impact of loss to follow-up or prospective patient recruitment. In this analysis, a series of LRE models was used to compare average HAQ scores over time for women with 1+, 2+ and 3+ APOs with the HAQ scores of women with no preonset APOs. Initially, these models were unadjusted and then subsequently progressively adjusted for the following: (1) age at symptom onset and symptom duration ('basic model'), (2) socioeconomic status and smoking status, (3) number of live births and CP use (before and during follow-up) and (4) number of comorbidities (counted at the chapter level of the *International Classification of Disease, 10th Revision*). Parous women with a history of APOs were subdivided by whether their most recent pregnancy before IP onset had been a live birth or an APO. An LRE model was then used to compare the HAQ scores of women in these two subgroups.

An interaction between each anniversary and APO history was included in the 'basic' LRE model to determine whether or not the association between APO history and HAQ score changed during the follow-up period.

As there were only three time points at which the DAS28 score was recorded, LRE analysis was carried out only for the subgroup of patients who had a DAS28 score at every time point, subsequently referred to as the 'DAS28 cohort'. LRE models as described above were constructed but with the DAS28 score as the measure of disease outcome. Again, the interaction between each anniversary and APO history was investigated.

**Table 1** Case-control studies of the association between history of APOs and RA

Authors, publication year (country)	Study population	Control population	Spontaneous abortion	Stillbirth	Induced abortion
			OR (95% CI) of a pregnancy resulting in APO rather than any other outcome (cases vs controls)		
Kay and Bach <sup>11</sup> , 1965 <sup>2</sup> (UK)	111	111 (community)	0.71 (0.4, 1.4)	0.68 (0.2, 2.7)	–
Kaplan, 1986 <sup>1</sup> (USA)	89	113 (osteoarthritis)	1.77* (1.2, 2.5)	–	0.15* (0.05, 0.5)
Silman <i>et al</i> <sup>1</sup> , 1988 <sup>3</sup> (UK)	40	67 (female relatives)	1.32 (0.6, 2.9)	10.1* (1.2, 85.4)	–
Siamopoulou-Mavridou <i>et al</i> , 1988 <sup>4</sup> (Greece)	72	98 (community)	1.42 (0.8, 2.4)	0.69 (0.2, 2.3)	–
Spector and Silman <sup>†</sup> , 1990 <sup>5</sup> (UK)	195	229 (community)	0.69 (0.4, 1.1)	1.78 (0.7, 4.7)	1.16 (0.6, 2.4)
Spector and Silman <sup>†</sup> , 1990 <sup>5</sup> (UK)	195	233 (osteoarthritis)	0.43* (0.3, 0.6)	1.31 (0.5, 3.2)	1.03 (0.5, 2.1)
OR (95% CI) of an individual having any history of APO (unless otherwise stated) (cases vs controls)					
Nelson <i>et al</i> , 1992 <sup>6</sup> (USA)	144	605 (community)	1 SA: 0.9 (0.6, 1.4) 2+ SA: 0.7 (0.3, 1.5)	0.9 (0.3, 2.7)	–
Symmons <i>et al</i> , <sup>†</sup> 1997 <sup>7</sup> (UK)	69	69 (community)	2.17 (0.9, 5.5)	–	–
Carette <i>et al</i> , 2000 <sup>8</sup> (UK)	55	165 (community)	–	–	3.74* (1.4, 9.9)

\*Significant difference.

<sup>†</sup>Not restricted by parity/gravidity.

<sup>‡</sup>Postmenopausal onset subcohort.

APo, adverse pregnancy outcome; SA, spontaneous abortion.

**Supplementary analysis including nulligravid women**

Two hundred and eighty-four nulligravid women who had been recruited to NOAR in the same period as the patients in the main analysis were added as a comparator group in an additional LRE model of HAQ scores. Patients were classified as follows: nulligravid, parous with no APOs (column 2 in table 2), 1–2 APOs and 3+ APOs (column 5 in table 2).

**RESULTS**

One thousand five hundred and eighty-nine gravid women were followed-up for a median of 5 years (IQR 1.6–8.4), and the total follow-up time was 8302 person-years. One thousand one hundred and ninety-two (75%) women in the cohort had no APOs before symptom onset. In total, the 397 (25%) women who had 1+ APO reported 547 SAs and 55 stillbirths before symptom onset. One hundred and twenty-five (8% of the whole cohort) women had 2+ APOs, and of these, 47 (3% of the whole cohort) had 3+ APOs. Among women with a history of APOs, the mean (SD) number of years between their most recent APO and symptom onset was 24 (13.5). The rate of stillbirths was 14.5

per 1000 reported births, and the SA rate per reported pregnancy was 12.6%.

The cohort characteristics are summarised in table 2. Women with a history of APOs were significantly younger at symptom onset than women with no APOs. The majority of women with a history of APOs were parous. Even among women with 3+ APOs, only 4% had not had at least one live birth. The number of live births was comparable by APO history. The proportion of women meeting the 1987 ACR criteria for RA was comparable between women with no APOs and women with 1+ APO. However, the proportion of women who satisfied the 1987 ACR criteria or who were RF positive at baseline increased with increasing number of APOs.

Unadjusted HAQ and DAS28 scores at baseline were not markedly different by APO history, although there was a small increase in DAS28 score with increasing number of APOs.

The results of LRE analysis are summarised in table 3, by APO history subgroups. The unadjusted mean difference in HAQ score, compared to women with no history of APOs, was not significant for any group. The mean difference in HAQ score was greatest for women who had 3+ APOs. The statistical interaction between ‘number of APOs’ and ‘follow-up anniversary’ was not significant in the LRE model. In other words, the mean difference in HAQ score by APO history was approximately the same at the 5th or 10th anniversary assessments as it was at baseline. Thus, the values reported in table 3 relate to the mean difference in HAQ score by APO history, averaged over all time points.

Adjustment for age at symptom onset and symptom duration had a marked impact on the estimates, suggesting that these factors were masking the relationship in the unadjusted model. The additional adjustments had little further impact, indicating that the relationship was probably not explained by these factors. Results from the maximally adjusted models show that, on average, the group of women who had 2+ APOs and the group who had 3+ APOs had significantly higher HAQ scores than women with no APOs.

To determine if this relationship remained significant in women meeting the 1987 ACR criteria for RA during follow-up, we introduced this factor as a statistical interaction in the maximally adjusted LRE model. The interaction was not significant ( $p=0.17$ ), which suggests that the relationship between APO history and HAQ score was not related to whether or not patients had RA.

Parous women who had at least one APO but no further live births following their most recent APO had comparable HAQ scores to women who did have a live birth after their final APO (mean difference 0.001; 95% CI 0.16 to 0.16).

**Table 2** Cohort characteristics at baseline

Cohort characteristics at baseline	No APOs (n=1189)	1+ APOs (n=397)	2+ APOs (n=125)	3+ APOs (n=47)
Age at symptom onset, years	55.1	51.5*	50.3*	50.8*
Median (IQR)	(45.9, 66.3)	(42.7, 61.5)	(40.6, 59.6)	(40.6, 58.3)
Symptom duration, months	6.4	7.7*	7.7	8.4
Median (IQR)	(3.0, 14.6)	(3.6, 17.2)	(3.3, 16.5)	(3.1, 18.0)
Parous before symptom onset	1189/1189	37 4/397	118/125	45/47
n/N (%)	(100)	(94)	(94)	(96)
Number of live births	2	2	2	2
Median (IQR)	(2, 3)	(2, 3)	(2, 3)	(2, 3)
Satisfy ACR criteria for RA	541/1189	181/397	63/125	26/47
n/N (%)	(46)	(46)	(50)	(55)
RF positive	307/1043	96/355	41/113	18/45
n/N (%)	(29)	(27)	(36)	(40)
HAQ score	1.01	1.01	0.97	1.02
Mean (SD)	(0.76) n=1176	(0.77) n=392	(0.79) n=123	(0.84) n=46
DAS28	3.88	3.84	3.91	4.07
Mean (SD)	(1.38) n=949	(1.41) n=316	(1.37) n=104	(1.26) n=42

\*Significant difference versus ‘No APOs’ ( $p<0.05$ ).

ACR, American College of Rheumatology; APO, adverse pregnancy outcome; DAS28, disease activity score; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; RF, rheumatoid factor.

**Table 3** Summary of three LRE models comparing mean HAQ score over time by APO history and number of APOs

	Mean difference in HAQ score†		
	1+ APO vs 0 APOs	2+ APOs vs 0 APOs	3+ APOs vs 0 APOs
Unadjusted model	−0.003 (−0.09, 0.08)	0.05 (−0.09, 0.19)	0.14 (−0.07, 0.36)
Basic model‡	0.04 (−0.04, 0.12)	0.12 (−0.01, 0.25)	0.21* (0.01, 0.41)
Additional adjustment: SES and smoking history	0.05 (−0.03, 0.13)	0.12 (−0.01, 0.25)	0.20 (−0.003, 0.41)
Additional adjustment: number of live births and CP use§	0.05 (−0.03, 0.13)	0.13 (−0.002, 0.26)	0.23* (0.02, 0.44)
Additional adjustment: comorbidities	0.05 (−0.03, 0.13)	0.13* (0.002, 0.26)	0.23* (0.02, 0.43)

\*Statistically significant ( $p<0.05$ ).

†Over the whole follow-up period.

‡Adjusted for age at symptom onset and symptom duration.

§CP use is either pre- or post-IP onset.

APO, adverse pregnancy outcome; CP, contraceptive pill; HAQ, Health Assessment Questionnaire; IP, inflammatory polyarthritis; SES, socioeconomic status.



**Table 4** DAS28 cohort characteristics at baseline

Cohort characteristics at baseline	No APOs (n=97)	1+ APOs (n=34)	2+ APOs (n=15)	3+ APOs (n=7)
Age at symptom onset, years	52.3	48.4	43.8*	51.8
Median (IQR)	(44.9, 60.0)	(38.6, 57.1)	(39.0, 51.8)	(49.4, 57.1)
Symptom duration, months	5.4	10.2	8.4	4.1
Median (IQR)	(2.1, 11.6)	(4.1, 18.7)	(2.5, 12.3)	(1.9, 9.0)
Parous before symptom onset	97/97	33/34	15/15	7/7
n/N (%)	(100)	(97)	(100)	(100)
Number of live births	2	2	2	2
Median (IQR)	(2, 3)	(2, 3)	(2, 3)	(1, 3)
Satisfy ACR criteria for RA	48/97	19/34	9/15	5/7
n/N (%)	(49)	(56)	(60)	(71)
DAS28	3.77	3.86	3.95	4.43
Mean (SD)	(1.38)	(1.45)	(1.68)	(1.74)

\*Significant difference versus 'No APOs' ( $p < 0.05$ ).

APO, adverse pregnancy outcome; ACR, American College of Rheumatology; DAS28, disease activity score; RA, rheumatoid arthritis.

There were 131 women for whom we could calculate a DAS28 score at baseline and at their 5th and 10th anniversary. The baseline characteristics of this DAS28 cohort are summarised in table 4. As in the whole cohort, women with no history of APOs were older at symptom onset than women with any APOs before symptom onset. All but one patient, who had 1+ APOs, were parous in the DAS28 cohort. More patients with a history of APOs met the ACR criteria for RA than patients with no APOs. The unadjusted mean baseline DAS28 score was lowest for women with no history of APOs and increased with number of APOs.

A summary of the LRE analysis with the DAS28 score as the outcome measure is shown in table 5. As with the HAQ score analysis, there was no significant interaction between number of APOs and follow-up anniversary in the LRE model. Therefore, the values in table 5 refer to the mean difference over the three time points.

Women with a history of APOs had higher DAS28 scores than women with no APOs, although this was only significant in the subgroups of women with 2+ or 3+ APOs. As the number of APOs increased, the mean difference in DAS28 score from women with no APOs also increased. Adjustment for age at symptom onset and symptom duration unmasked a significant difference between women with 2+ APOs and women with none. The difference for the whole group of women with any history of APOs was not statistically significant in either model, and the difference between women with 3+ APOs and women with no history of APOs was statistically significant in the adjusted and unadjusted models.

### Results of supplementary analysis

Compared to nulligravid women, gravid women who had either no APOs or  $\leq 2$  APOs had significantly lower HAQ scores (table 6). Women with 3+ APOs had comparable HAQ scores to nulligravid women and significantly higher HAQ scores than parous women with no history of APOs.

### DISCUSSION

This investigation has shown that, on average, women with 2+ APOs before IP onset have a poorer functional outcome than women with no history of APOs. The relationship was most pronounced in women with 3+ APOs. There is also some evidence for the same relationship between APO history and disease activity. Our findings add another dimension to the previous report from

**Table 5** Summary of three LRE models comparing mean DAS28 over three time points by APO history and number of APOs

	Mean difference in DAS28 <sup>†</sup>		
	1+ APO vs 0 APOs	2+ APOs vs 0 APOs	3+ APOs vs 0 APOs
Unadjusted model	0.29 (−0.10, 0.68)	0.47 (−0.07, 1.01)	0.96* (0.21, 1.72)
Basic model <sup>‡</sup>	0.34 (−0.05, 0.73)	0.56* (0.01, 1.11)	0.98* (0.23, 1.74)

0 APOs: n=97; 1+ APOs: n=34; 2+ APOs: n=15; 3+ APOs: n=7.

\*Statistically significant ( $p < 0.05$ ).

<sup>†</sup>Over baseline and at the 5th and 10th anniversaries.

<sup>‡</sup>Adjusted for age at symptom onset and symptom duration.

APO, adverse pregnancy outcome; DAS28, disease activity score.

the Netherlands of a faster rate of radiographic progression seen in female patients who have early RA with a history of SA.<sup>10</sup>

Women with a history of APOs were younger at IP symptom onset than women with no APOs. Adjustment for age at symptom onset and symptom duration 'unmasked' an association between APO history and HAQ score. It is possible that women who were younger at symptom onset were more likely to recall APOs before symptom onset than women who were older at symptom onset. However, as the difference in median age at symptom onset was only around 5 years, it is perhaps more likely that a history of APOs is associated with IP risk in this cohort, bringing forward the date an individual develops IP.

The rate of stillbirths in our cohort (14.5 per 1000 births) is marginally higher than that of the general population of England and Wales in 1969 (13.2 per 1000 births), which corresponds to the median year of pregnancy in our cohort.<sup>16</sup> The stillbirth rate in the UK during the years 2007–2009 has been estimated as 3.4 per 1000 births. In the 14 years between 1995 and 2009, the rate of stillbirths in 'high-income' countries had fallen by just over 20%.<sup>17</sup> This highlights the importance of revisiting this topic over time, as patterns in the incidence of APOs change. The recruitment of women with different calendar years of peak reproductive activity may also partially explain differences in the findings of case-control studies of APO history and subsequent RA development (table 1). The self-reported SA rate in our cohort (13% of pregnancies) was comparable to the range of rates reported among control patients with no RA (8–20%) in English case-control studies of APOs as a risk factor for subsequent development of RA.<sup>2 3 5 18</sup> Data regarding the national SA rate for the UK were not available.

This is the largest prospective study to investigate the relationship between preonset APOs and disease outcome in women with recent-onset IP. This is the first time that LRE modelling has been used to assess the relationship between APO history and disease outcome over time. By using this longitudinal analytical technique, we were able to adjust for the highly correlated nature of repeated measures of HAQ and DAS28 score.

Adjustment for potential confounders had little impact on the estimates produced, suggesting that the relationship between APO history and disease outcome was robust. The mean difference in HAQ score between women with 3+ APOs and women with no APOs reported here (mean difference 0.23) was greater than the generally accepted minimal clinically important difference of 0.22 for HAQ.<sup>19</sup>

Patients recruited to NOAR have IP, which is a broader category than RA alone. The NOAR cohort is thus potentially more heterogeneous than a cohort of patients with RA. However, 75% of NOAR patients have been shown to fulfil the 1987 ACR criteria for RA within 5 years of symptom onset.<sup>20</sup> In addition, we found no evidence of an interaction between RA status and APO history. These results are therefore generalisable to women with IP who have RA and those who do not have RA.

**Table 6** Mean difference in HAQ score by reproductive history before IP onset

	Comparator	
	Nulligravid (n=284)	Live births only (n=1189)
	Mean difference in HAQ scores over time (95% CI)	
n=1189 live births only versus	-0.19* (-0.33, -0.05)	-
n=350 1-2 APOs versus	-0.15* (-0.30, -0.01)	0.04 (-0.05, 0.12)
n=47 3+ APOs versus	0.03 (-0.21, 0.27)	0.22* (0.01, 0.43)

\*Significant difference.

APO, adverse pregnancy outcome; IP, inflammatory polyarthritis; HAQ, Health Assessment Questionnaire.

One limitation of this study is the low number of patients in the DAS28 cohort, especially those with 3+ APOs. Our findings with respect to DAS28 score need to be replicated in a larger cohort and with more measurements per individual.

Reliance upon patient reports of pregnancies and their outcomes is another limitation of this study, as it was not possible to verify reports using medical records. Having said this, early SAs may not be recorded in medical records, and patient recall of their pregnancies and outcomes has been shown to have 'good to excellent' agreement with medical records.<sup>21</sup>

We included only gravid women in our study, as there are a number of physiological and non-physiological reasons why an individual may have never been pregnant. Another consideration when interpreting our findings was that we did not include IAs as an APO in this analysis. We have previously found that they are under-reported in the setting of a face-to-face interview.<sup>8</sup> Therefore, women who reported one or more IAs but no other pregnancies were excluded from this analysis.

The exact mechanism by which APOs may be associated with subsequent IP disease outcome is unknown. There are a number of possible explanations. It may be that women who are genetically predisposed to develop IP are also predisposed to APOs. In this case, the APO would not be a direct cause of the poor IP outcome but a marker of an underlying immunological or physiological abnormality. Women who are predisposed to develop IP may be less able, immunologically, to tolerate the allogeneic tissue of a fetus, resulting in SA or stillbirth, or it could be that the cytokine profile of these women is more likely to lead to a poor pregnancy outcome and worse IP.<sup>10</sup>

Patients with RA may be autoantibody positive for many years before symptom onset.<sup>22</sup> Thus, changes in the immune system that increase the likelihood of an APO, and later result in IP/RA, may also begin many years before symptom onset. We attempted to repeat our analyses in the subgroup with RF, but the number of patients was too small to produce meaningful estimates (data not reported).

Alternatively, it may be the APO itself (either immunologically or psychologically) that primes the woman to subsequently develop IP, and for that IP to appear more aggressive. For that reason, it would be interesting to study the relationship between IAs and IP outcome. If the majority of terminated pregnancies would have resulted in a live birth, IAs may be associated with a lesser impact on subsequent disease outcome than the APOs studied here. However, it may also be the case that IAs and other APOs have the same relationship with disease outcome; discontinuation of pregnancy by any means may be responsible for the effect observed here. Our findings suggest that having a subsequent live birth after having an APO did not attenuate the impact of any residual physical or psychological change as a result of having had an APO, which may influence IP disease outcome.

We found evidence of a 'dose-response effect' in that the proportion of women who were RF positive at baseline increased with increasing number of APOs. This makes it more likely that the observed association is 'real' but is equally compatible with the hypothesis that a common abnormality predisposes to APOs and IP and not that the APO itself brings about the abnormality that leads to worse IP.

In a previous investigation, we reported that women who had at least one live birth before IP onset had lower HAQ scores over time on average than nulliparous women.<sup>23</sup> The supplementary analysis reported as part of the current investigation indicated that nulligravid women and gravid women with a history of three or more APOs had comparable HAQ scores over time that were higher on average than the HAQ scores of women who had one or two APOs (94% of whom were parous) and women who had live births only. This suggests that whatever the underlying mechanisms, the benefit associated with having a live birth is greater than the negative impact associated with having one or two APOs but not greater than the combined impact of having multiple APOs.

We have also previously reported that pregnancy during follow-up was associated with a positive impact on functional outcome, although in that analysis, the outcome of those pregnancies was not investigated.<sup>24</sup> Further work investigating the relationship between APOs after symptom onset and disease outcome is needed.

In conclusion, we have found that after adjustment for age and symptom duration, gravid women with a history of two or more APOs prior to IP onset have a worse prognosis than gravid women with a history of one or no APO. There is a dose-response effect with an increasing number of APOs being associated with a worse prognosis. The association was statistically robust and relatively stable over time. Further studies are needed to try and unravel the mechanisms underlying this observation.

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**Competing interest** None.

**Patient consent** Obtained.

**Ethics approval** The Norfolk Arthritis Register was conducted with the approval of the Norwich research ethics committee.

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