

EXTENDED REPORT

Pregnancy and oral contraceptive use do not significantly influence outcome in long term rheumatoid arthritis

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Background: Oral contraceptives (OC) and pregnancy are known to have an influence on the risk of onset of rheumatoid arthritis (RA). Pregnancy itself has beneficial effects on the activity of the disease, with relapses post partum. It is not known, however, whether OC and pregnancies influence the ultimate outcome of RA.

Objectives: To explore whether OC use and pregnancies influence the 12 year outcome in RA as measured by radiological damage and disability.

Methods: In a prospective inception cohort of 132 female patients with recent RA according to the 1987 American College of Rheumatology criteria—a cohort initially gathered to study the association between hormonal factors and the onset of RA—outcome was assessed in a follow up after 12 years. The outcome was evaluated in 112 (85%) women by the radiological damage of hands and feet as measured with the Sharp score modification van der Heijde (SHS), the damage of the large joints measured with the Larsen score (LS) of large joints (0–60), and the disability measured with the Health Assessment Questionnaire (HAQ). The median values of each outcome variable were calculated for several subgroups of patients stratified for OC use and pregnancies before and after onset of the disease and the tertiles of the total number of months of OC use and of pregnancies. The association of OC use and pregnancies before and after onset of the disease with the outcome variables was calculated using Spearman's rank correlation (r_s). The combined influence of OC use and pregnancies on the SHS, LS, and HAQ at 12 years was estimated using ordinal polytomous logistic regression.

Results: The median values of the SHS, LS, and HAQ showed a trend towards less radiological joint damage and less disability in women with long term OC use and multiple pregnancies. This difference, however, was not significant, except for the HAQ score in women with three or more pregnancies in life. There was no association between pregnancies, however defined, and any parameter of RA outcome after 12 years (maximum r_s = -0.10). The only significant correlation was found between OC use before symptom onset and the LS (r_s = -0.22, $p < 0.05$). The combination of hormonal variables explained no more than a maximum of 3% of the variance of the 12 year outcome as measured by the SHS.

Conclusion: OC use and pregnancy do not significantly influence outcome in long term RA. There is, however, a trend for patients with multiple pregnancies and long term OC use to have less radiographic joint damage and a better functional level.

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The relationship between rheumatoid arthritis (RA) and female sex hormones has long intrigued clinicians. There is a dual relationship between the two. Women, particularly women in their reproductive years, are more susceptible to RA than men.¹ On the other hand, it has been suggested that the onset of RA is postponed by parity, the risk of onset is reduced during pregnancy, while in the first year post partum the chance of onset is increased.² Moreover, the disease itself is also influenced by pregnancy. Several studies showed that disease activity decreased in 50–75% of women with RA during pregnancy, 16% even achieved complete remission, and many were able to stop all drugs by the last trimester. After delivery, disease activity predictably returned.³

An explanation for the amelioration of the disease activity during pregnancy may be the increased immune tolerance during that period. The immunological changes related to pregnancy are thought to be due to the maternal exposure to fetal (paternal) antigens. Nelson *et al* noted an increased number of HLA class II incompatibilities between mother and child among women with diminished activity of RA during pregnancy.⁴ Moreover, a shift towards Th2 cells was seen during pregnancy, which also might influence the level of disease activity.⁵

The overall effect of the changes during gestation and post partum on long term outcome in RA is insufficiently known.

One retrospective analysis showed no influence of pregnancy on functional capacity, disease activity, erosive arthritis, and erythrocyte sedimentation rate (ESR) in a long term follow up.⁶ As far as we know, no prospective data on the effect of pregnancy on long term outcome in RA are available. Several mechanisms have been proposed to explain the influence of female sex hormones on the onset and course of RA.⁶ Studies in vivo and in vitro have shown that sex hormones interfere with immunoregulation, interact with inflammatory mediators, and have direct effects on the cartilage itself. All these observations point towards the importance of gonadal hormones in immunoregulation.

Oral contraceptives (OC) have been thought to protect against the more severe forms of RA.^{8–10} The influence of OC use on the long term outcome in RA is not known.

The aim of the present study was twofold. Firstly, to study whether OC use or pregnancies before and after onset of RA are associated with long term radiological joint damage or

Abbreviations: DMARD, disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; JSN, joint space narrowing; LS, Larsen score; OR, odds ratio; RA, rheumatoid arthritis; SHS, Sharp score modification van der Heijde score

disability; and, secondly, to estimate the combined influence of OC use and pregnancies on radiological joint damage and disability

PATIENTS AND METHODS

Patients

The present patient cohort has been extensively described in previous reports.^{9–11,12} The patients were gathered together for a case-control study of the association between hormonal factors and RA.^{11,12} In total, 138 consecutive incident female patients with RA visiting the outpatient rheumatology clinic of the Leiden University Medical Centre for the first time between 1982 and 1986 with symptoms of recent onset (0–5 years) and aged 20–50 years at first visit were included in the study. Of the 138 patients invited to participate, three initially refused to cooperate and three were lost during the first years as they moved out of the area. One hundred and thirty two women were prospectively followed up for 12 years. Data were collected at the start of the study, yearly in the first six years and, finally, at the follow up after 12 years. Because the patients had their final assessment done over a two year period, not all patients were assessed at exactly 12 years of follow up. The median disease duration at the last follow up visit was 12 years (range 10–14). This final assessment will be referred to as the 12 year follow up assessment.

Hormonal factors

At the start of the study detailed information on OC use was collected, including dates and duration of use in monthly periods. A life calendar with major life events when contraceptive use might begin (for example, engagement, marriage, childbirth) and a tray with examples of OC packages available in the Netherlands from 1960 to that date were used to help women recall their use of contraceptives. The records of their general practitioners were checked if a patient could not give complete information. Pregnancies before the onset of RA were recorded. At all assessments the number of months of OC use and the number of pregnancies during the previous period were recorded.

Disease activity

At baseline the number of swollen joints, the Ritchie articular index,¹³ and the Westgren ESR scores were obtained as parameters of disease activity. The disease activity score (a pooled index of the ESR, the number of swollen joints, and the Ritchie articular index) was calculated as a combined index of disease activity.¹⁴

Radiology

Radiographs of the hands and feet were taken at study start and after 12 years of follow up and scored using the Sharp score modification van der Heijde (SHS).¹⁵ The SHS separately identifies joint space narrowing (JSN) and erosions in the metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints and two interphalangeal joints of the big toes. The joint of the thumb has only an erosion score. Furthermore, six areas in each wrist are assessed for JSN and six others for erosions. The narrowing in both hands and feet is scored from 0 to 4 for each joint. The maximum erosion score in the hands is 5, in the feet 10. The maximum score for the SHS thus is 448: 168 for JSN, 280 for erosions.

After the 12 years' follow up, radiographs of shoulders, elbows, hips, knees, ankles, and subtalar joints were scored according to the Larsen score (LS) for large joints.¹⁶ A score of 1 was given in cases of slight JSN, but not in case of soft tissue swelling and/or osteoporosis only. Larsen scores of 2–5 were given in case of erosive disease; higher scores indicating more damage. In weight bearing joints erosions are not obligatory for Larsen grade 2. The presence of a total joint replacement or an arthrodesis was graded with the maximum score of 5. The

total LS is calculated by summing all the scores of the separate joints and ranges between 0 and 60.

Physical functioning

The Health Assessment Questionnaire (HAQ) is used as the parameter for physical functioning and was adapted for the Dutch population.¹⁷ The questionnaire consists of eight categories and the responses are scored on a four point scale. The questionnaire has a final column in which respondents can indicate the use of any aid or device. The use of one of these is scored by at least a 2. The highest score of each category is taken as the score for that category. The final score of the questionnaire is the averaged score of all the categories, and ranges between 0 and 3.

Analysis

To see whether there were baseline differences between patients with or without OC use or with or without pregnancies, the baseline variables were compared between these groups of patients. Differences were tested for significance using Student's *t* test or Mann-Whitney test, where appropriate.

Outcome at 12 years was also compared between these subgroups. In addition, the effects on outcome of pregnancies and OC use before RA onset, and during RA were evaluated.

The effect of OC use and pregnancies on outcome was further studied by separating the sample into subgroups of patients based on the tertiles of total months of OC use and on the tertiles of the number of pregnancies. In all cases we used non-parametric test statistics.

Finally, Spearman rank correlations and ordinal polytomous logistic regression were used to analyse the association between outcome variables and several hormonal parameters.

RESULTS

Table 1 shows the demographic and baseline variables. There were no statistically significant differences between the groups except for the age of disease onset between patients with or without OC use. Furthermore, there was also no difference in baseline variables, including OC use and pregnancies, between the women studied and those lost to follow up.

The median duration of OC use before the onset of RA was 60 months (range 0–248) and during the course of the RA the median duration of OC use was 34 months (0–144). The median of the total duration of OC use was 94 months (0–392). The median number of pregnancies was 2 (0–8) before the onset of RA and 0 (0–4) during the course of RA. The median of the total of pregnancies was 2 (0–8).

Table 1 Baseline characteristics of 112 female patients with RA stratified by ever pregnancy and ever OC use (combined before and during RA). Results are given as means (SD)

	Parity ever		OC use ever	
	No	Yes	No	Yes
Number of patients	21	91	33	79
Age	39 (9.4)	38 (8.3)	40 (7.9)*	36 (8.2)
Duration symptoms	1 (2.7)	1 (3.0)	1 (3.0)	1 (3.0)
DAS	3.0 (1.5)	2.9 (1.2)	2.6 (1.9)	2.9 (1.3)
RF positive (%)	71	68	69	68
SHS	0 (8.7)	0 (5.5)	0 (4.8)	0 (6.0)
HAQ	0.88 (1.5)	0.63 (1.1)	0.62 (1.2)	0.63 (1.1)

DAS, disease activity scale; RF, rheumatoid factor; SHS, Sharp score modification van der Heijde; HAQ, Health Assessment Questionnaire.

**p*<0.02, Mann-Whitney.

Table 2 Median values (range) of the outcome variables for radiographic joint damage as measured with the SHS and Larsen score of large joints and disability as measured with the HAQ in subgroups with respect to OC use and pregnancies before and during RA in female patients at 12 years of follow up

	Number of patients	SHS	Larsen	HAQ
OC use before RA*				
-	30	148 (0-392)	6.5 (0-34)	1.0 (0-2.63)
+	82	117 (0-428)	3.0 (0-55)	0.87 (0-3)
OC use during RA*				
-	58	146 (0-392)	5 (0-48)	1.0 (0-2.88)
+	54	78 (0-428)	3 (0-55)	0.75 (0-3)
Pregnant before RA*				
-	33	145 (0-413)	3 (0-48)	1.0 (0-2.88)
+	79	123 (0-428)	3 (0-55)	0.62 (0-3)
Pregnant during RA*				
-	88	145 (0-428)	3 (0-55)	1.0 (0-3)
+	24	56 (0-395)	3 (0-31)	0.87 (0-2.25)

SHS, Sharp score modification van der Heijde; Larsen, Larsen score for large joints (0-60); HAQ, Health Assessment Questionnaire.
*Differences between - and + not significant according to Mann-Whitney.

Table 2 shows the outcome variables for radiographic joint damage and disability in the four subgroups of patients. The patients who either used OC or had been pregnant had less radiographic joint damage of the small and large joints, but this difference did not reach statistical significance. Disability as measured by the HAQ was less in the group with OC use and pregnancies; in the group of women who had been pregnant before the onset of RA the difference in HAQ was the largest (0.38).

By further study possible differences in outcome between groups, the medians of the SHS, Larsen, and HAQ, were calculated for each tertile of cumulative OC use and of cumulative pregnancies (table 3). Again the patients within the highest tertile of pregnancies or months of OC use had less radiological damage and less disability. Patients who had been pregnant three or more times had significantly less disability than those who had not been pregnant.

The Spearman rank correlations of the outcome parameters with the exposure to pregnancy or cumulative OC use were calculated. Only the association of OC use before the onset of RA with the LS of large joints was statistically significant. After checking for age, rheumatoid factor, and SHS at onset, the association became non-significant.

When polytomous logistic regression analysis on the tertiles of the SHS distribution was used, the (pseudo) R^2 of the combined influence of OC use and pregnancies was only 0.026. Neither number of pregnancies (odds ratio (OR)=0.96, $p=0.70$) nor months of OC use (OR=0.99, $p=0.11$) were significantly related to SHS tertile.

DISCUSSION

This study shows that OC use and pregnancy only minimally influence the long term outcome in RA as assessed by joint damage and disability. There is, however, a trend towards less joint damage and disability in patients with long term OC use and multiple pregnancies.

The study shows that the median HAQ score in women with a total of two pregnancies during life is 0.63 lower than the score in women with no child or one. A difference between HAQ scores of more than 0.2 is considered clinically relevant.¹⁸ The trend towards less radiographic joint damage and less disability in women with long OC use is noticeable because the women in the OC use group were significantly older than the group without OC use. Disability in RA has been shown to be greater in older patients, so the trend towards less disability in the older patients with long OC use is even more remarkable. Disease modifying drug (DMARD) use influences outcome and was shown to have a beneficial effect on radiographic damage and function. All women were similarly treated by the less aggressive standard of two decades ago. Women who wanted to get pregnant often discontinued drug treatment. Therefore the trend towards less radiographic damage and disability is not likely to be due to DMARD use. The trend towards a milder disease in the group of patients with a high exposure to female sex hormones, however, did not show statistical significance, which might be owing to a lack of power. This is not surprising considering the large ranges of the outcome variables (table 2 and 3). Three hundred and thirty female patients divided into two subgroups would be needed to reach statistical significance, given the data of the present study and the trend found. In the univariate analysis the associations were not strong. Moreover, in a multivariate analysis the combined influence of OC use and pregnancies explained no more than at most 4% of the variance of the 12 year outcome as measured by the SHS, LS, or HAQ.

Pregnancy was first reported to induce remission in RA in 1935.¹⁹ Since then, many studies have reported the ameliorating effect of pregnancy on disease activity. As a possible explanation for this phenomenon it has been suggested that levels of endogenous female hormones influence the disease. This

Table 3 Median values (range) of the outcome variables for radiographic joint damage as measured with the SHS and Larsen score for large joints, and disability as measured with the HAQ in subgroups with respect to tertiles of exposure to OC use in months and number of pregnancies in female patients with RA at 12 years of follow up

	Number of patients	SHS	HAQ	Larsen
Total OC use				
<40 months	37	146 (0-392)	1.0 (0-2.63)	6 (0-48)
40<x<150	36	157 (0-395)	0.87 (0-2.88)	2.5 (0-55)
>150 months	37	74 (0-428)	0.5 (0-3)	3 (0-48)
p*		0.196	0.96	0.34
Pregnancies (n)				
<2	26	131 (0-413)	1.25 (0-2.88)	3 (0-48)
2	45	78 (0-428)	0.62 (0-3)	3 (0-40)
≥3	39	145 (0-395)	0.75 (0-2.63)	4.5 (0-55)
p*		0.75	0.05	0.296

SHS, Sharp score modification van der Heijde; Larsen, Larsen score for large joints (0-60); HAQ, Health Assessment Questionnaire.
*Lowest versus highest tertile Mann-Whitney.

view was further strengthened by the finding that OC use had a protective role in the incidence of RA and also had a restraining influence on the course of the disease.^{7 11 20} In one study on hormone treatment in RA some improvement was reported in disease activity when oestrogen was given.²¹ In view of this evidence it was plausible that the long term outcome of RA might be influenced by female sex hormones. Our study, however, shows that hormonal parameters contribute only minimally to the explanation of long term radiological damage and disability.

This is the first prospective long term outcome study to investigate the association between hormonal factors and joint damage. One other study reported the long term outcome in RA. In 1966 Oka described a retrospective case control study in a group of 100 consecutive patients who had been pregnant after the onset of RA.⁶ These women were compared with an equal number of women who had not been pregnant since developing RA. In that study, which comes with the usual limitations of a retrospective study, no significant differences were found in functional ability or disease activity. This is in accordance with the present study.

In conclusion, this study shows that OC use and pregnancy do not significantly influence outcome in RA. There is, however, a trend for patients with multiple pregnancies and long term OC use to have less radiographic joint damage and a better functional level. This information is important in counselling young women with RA.

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