

Original article

Fertility in women with chronic inflammatory arthritides

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Abstract

Objective. To compare fertility rates in women with RA, other chronic arthritides (OCAs) and JIA with reference women from the general population.

Methods. Each woman from a Norwegian patient registry was matched by year of birth with 100 reference women randomly selected from the National Population Registry. Data linkage of patients and references with the Medical Birth Registry of Norway (MBRN) identified all offspring in patients and references until October 2007, and indirectly also nulliparous (childless) women. Groups were compared with Mann–Whitney U-test for continuous variables and chi-squared tests for categorical variables. Poisson regression analysis was applied to calculate relative fertility rates in the diagnostic groups vs references.

Results. Among 631 patients 849 children were registered in MBRN. Of these, 289 children (34.0%) were born after time of diagnosis vs 44.3% in references. Altogether, 206 of 631 patients (32.6%) were nulliparous vs 26.4% in references ($P < 0.001$). Among RA patients, 28.4% (96 of 338) were nulliparous vs 24.5% in references ($P = 0.09$), 30.7% (67 of 218) in OCA patients vs 24.5% in references ($P = 0.03$) and 57.3% (43 of 75) in JIA patients vs 40.9% in references ($P = 0.004$). Adjusted relative fertility rates in RA, OCA and JIA after diagnosis were 0.88, 0.84 and 0.84, respectively, compared with references.

Conclusion. A higher proportion of women with chronic inflammatory arthritides were nulliparous compared with references, and relative fertility rates were reduced in all patient groups.

Key words: National registry, Fertility rate, Number of births, Inflammatory rheumatic disease.

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Introduction

Chronic inflammatory arthritides (CIAs) may influence the production of offspring (fertility) due to different mechanisms: physical, psychological, hormonal or immunological as well as medical treatments [1].

Fertility has particularly been studied in RA. Some studies have indicated reduced sexual desire and lower frequencies of intercourse in women with RA [2–4]. In a report with structured interviews of ~400 married women with RA, nearly one in five patients answered that RA influenced childbearing decisions, and especially in women diagnosed at a young age [5]. The overall percentage of women having children was not different from the general population, but women with RA were more likely to opt for a single child.

Data obtained in cross-sectional surveys have suggested low ability to conceive a child and longer time to achieve pregnancy in RA patients, both before and after

disease onset [6, 7]. However, a case-control study with age-matched controls did not find any association between RA and low fertility [8].

Few publications exist on fertility in other chronic arthritides (OCAs). In AS, three studies have reported normal fertility [9–11], but longer time to achieve pregnancy has been reported in one study [11].

Women diagnosed with JIA may experience long-term physical and psychosocial impairment [12]. In one study, fertility was not impaired in JIA women [13], but longer time to achieve pregnancy has been reported [13, 14].

Previous studies have examined fertility in heterogeneous patient groups, from the worst to the mildest affected women. We wanted to study fertility among the most severely affected patients, i.e. women treated with synthetic or biological DMARDs. The aim of the study was to compare fertility rates in women with RA, OCAs and JIA with birth-year-matched references from the general population.

Material and methods

Setting

Since 2001 data of patients with CIA have been recorded in the Norwegian DMARD (NOR-DMARD) registry. Patients are enrolled when they start with a synthetic or biological DMARD, but many of the patients have been diagnosed and have used DMARDs several years before enrolment. The NOR-DMARD registry has previously been described in detail [15].

Since 1967, medical data on all births in Norway have been recorded in the Medical Birth Registry of Norway (MBRN) [16, 17]. From 1967 to 1998 the registry collected data on all births in Norway after 16 weeks of gestation. Since 1999, all births after 12 weeks of gestation have been registered. The records include demographic data on the parents and their reproductive history.

The study was performed in accordance with the Helsinki Declaration and approved by the Norwegian Data Inspectorate, the Regional Ethics Committee of Central Norway and the Norwegian Directorate of Health. Permission to use references from the Norwegian Population Registry was approved by the Norwegian Tax Authorities and the Regional Ethics Committee of Central Norway.

Patients

Patients from the NOR-DMARD registry enrolled during 2001–06 were included in the present cohort study. All patients had signed a written informed consent form before enrolment. In addition, eligible women received written information about the planned linkage of NOR-DMARD data and MBRN. Fourteen women opted out, and data of 631 women from the NOR-DMARD registry were linked with the MBRN including deliveries until October 2007. All patients were diagnosed by a rheumatologist before or at enrolment in the NOR-DMARD registry.

Due to low numbers, the women with PsA, AS and unspecified arthritis (UA) were analysed as an entity labelled OCAs. UA comprised patients without fulfilment of criteria of a specified arthritis. Thus, the study population included 338 women with RA, 218 with OCA and 75 adult patients with JIA, all diagnosed before 45 years of age (JIA before 16 years of age).

Time of diagnosis was recorded by a rheumatologist when the patient was enrolled in the NOR-DMARD registry. Data on maternal age at delivery, birth order, date of last menstrual period, date of birth and gestational age were retrieved from MBRN. Nulliparous (childless) women were identified by lack of match in MBRN. Interpregnancy interval was defined as the time period from the date of the first birth to the first day of the last menstrual period preceding the second birth.

Reference population

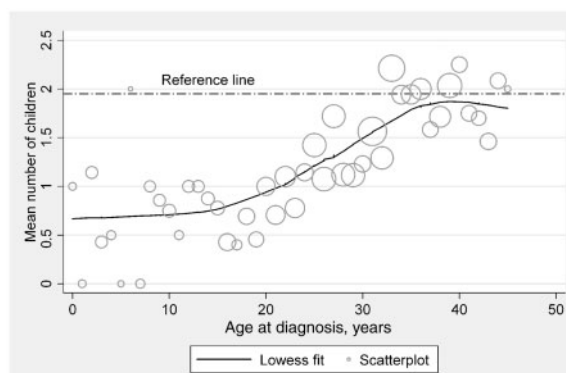
Each patient was matched by year of birth with 100 reference women randomly selected from the Norwegian Population Registry, with a total of 63 100 references. All references were linked to the MBRN to identify all offspring.

Analysis

For group comparisons, Mann-Whitney U-test was used for continuous variables and chi-squared test for categorical variables. Date of diagnosis for each patient was linked to the corresponding references to analyse pre- and post-diagnosis parity. Poisson regression analysis was applied to estimate relative fertility rates in women with RA, OCA and JIA, before and after diagnosis vs birth-year-matched references with adjustment for birth order at the time of diagnosis when relevant.

Regression analysis by locally weighted scatterplot smoothing (LOWESS fit) was used to calculate and visualize mean number of children by age of diagnosis (Fig. 1). Cox regression analysis with adjustment for maternal age

Fig. 1 Mean number of children in all patients with CIAs by age at diagnosis. Lowess fit: regression line. Scatterplot: mean number of children, size weighted for the number of patients diagnosed per year.



at first delivery was used to compare the interval between first and second birth in patients and references.

Two-sided $P < 0.05$ was interpreted as significant. Data were analysed using the Statistical Package of Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA) and Statistics/Data Analysis (STATA), version 11.0 (StataCorp, College Station, TX, USA).

Results

Among the 631 patients, 849 children were registered in MBRN. Of these, 289 children (34.0%) were born after the time of diagnosis vs 44.3% in references. In the diagnostic groups, 147 children were registered in the RA group, 89 in the OCA group and 53 in the JIA group after diagnosis (Table 1).

Altogether 206 of 631 (32.6%) patients were nulliparous vs 26.4% in references ($P < 0.001$) at the time of censoring (October 2007). Among RA patients 28.4% (96 of 338) were nulliparous vs 24.5% in references ($P = 0.09$), 30.7% (67 of 218) in OCA patients vs 24.5% in references ($P = 0.03$) and 57.3% (43 of 75) in JIA patients vs 40.9% in references ($P = 0.004$) (Table 1).

Mean number of children was lower in patients than references (Fig. 1). Especially, this difference was marked in women diagnosed before 30 years of age. In women diagnosed after the age of 30 years, mean number of children approached that of the age-matched references.

Adjusted relative fertility rates in RA, OCA and JIA after diagnosis were 0.88, 0.84 and 0.84, respectively (Table 2). Relative fertility rates in patients before diagnosis were not reduced (Table 2).

In the analyses of inter-pregnancy interval, 38 patients had their first delivery before they received a diagnosis of CIA and the second delivery after diagnosis (Table 3). Further, 70 patients had all deliveries after the time of diagnosis. We observed significantly increased inter-pregnancy intervals in RA and OCA women diagnosed between first and second birth. No differences in the intervals were observed in any of the diagnostic groups with both first and second birth after diagnosis (Table 3).

TABLE 2 Relative fertility rates (RFRs) in patients from the NOR-DMARD registry vs references, before and after diagnosis

Group	RFR (95% CI)	P-value
After diagnosis		
RA		
Crude	0.88 (0.83, 0.93)	<0.001
Adjusted ^a	0.88 (0.84, 0.93)	<0.001
OCA		
Crude	0.84 (0.78, 0.90)	<0.001
Adjusted ^a	0.84 (0.78, 0.90)	<0.001
JIA	0.84 (0.77, 0.92)	<0.001
Before diagnosis		
RA	0.99 (0.96, 1.03)	0.89
OCA	0.99 (0.95, 1.04)	0.78

^aAdjusted for birth order.

TABLE 1 CIA patients with references in diagnostic subgroups with numbers of nulliparous women, total number of deliveries and mean number of deliveries per woman

Group	Patients, <i>n</i>	Nullipara, <i>n</i> (%)	Total number of deliveries and mean number of deliveries per woman			Mean age at the time of data linkage, years	
			Total	Before diagnosis	After diagnosis	Para 1+	Nullipara
Total patients	631	206 (32.6)	849	560	289	NS	NS
			1.35	0.89	0.46		
Total references	63 100	16 658 (26.4)	101 728	56 670	45 058	NS	NS
			1.61	0.90	0.71		
RA patients	338	96 (28.4)	501	354	147	41.1	36.7
			1.48	1.05	0.43		
RA references	33 800	8281 (24.5)	56 870	35 656	21 214	41.0	36.3
			1.68	1.05	0.63		
OCA patients	218	67 (30.7)	295	206	89	40.7	35.2
			1.35	0.94	0.41		
OCA references	21 800	5341 (24.5)	35 928	21 013	14 915	39.9	36.1
			1.65	0.96	0.68		
JIA patients	75	43 (57.3)	53	0	53	38.2	29.9
			0.71		0.71		
JIA references	7500	3067 (40.9)	8930	0	8930	36.1	29.5
			1.19		1.19		

NS: not stated.

TABLE 3 Inter-pregnancy interval^a in relation to time of diagnosis

Group	Age at first delivery, patients, years, mean	Age at first delivery, references, years, mean	P-value	Median interval, patients, years	Median interval, references, years	P-value
First birth before diagnosis, second birth after diagnosis RA (n = 22)	25.3	25.3	0.90	3.5	2.3	0.004* 0.003**
OCA (n = 16)	25.3	25.3	0.91	4.6	2.1	0.001* 0.002**
First and second birth after diagnosis RA (n = 36)	28.1	25.2	<0.001	2.6	2.2	0.33* 0.82**
OCA (n = 17)	26.9	25.2	0.09	1.9	2.2	0.64* 0.74**
JIA (n = 17)	25.0	25.2	0.94	2.5	2.3	0.56* 0.39**

^aAnalysis on single births. *Crude; **adjusted for maternal age at first delivery. OCA: OCAs such as PsA, AS and UA combined.

Discussion

In this study of CIA patients treated with synthetic or biological DMARDs, a higher proportion of patients were nulliparous compared with age-matched references ($P < 0.001$). When examining each diagnostic group separately, the proportion of nulliparity reached statistical significance for patients diagnosed with OCA and JIA, but not for RA women. The high proportion of nulliparous women among JIA patients and references was probably due to the younger age of this group with a mean age of ~30 years at the time of data linkage (Table 1). Only three previous studies of RA patients have reported the proportion of nulliparous women [6, 8, 18], and all with an excess of nulliparity among patients. Nulliparity has been discussed as a risk factor for RA [6, 18–22], but to our knowledge nulliparity has not been discussed as a risk factor for OCA.

More likely, our observation of a higher proportion of nulliparity among CIA patients may be caused by non-remitting disease and functional impairment, which have previously been reported to reduce the wish for children in women with CIA [5, 14]. Also, severe disease flares have been reported to lower sexual activity [23, 24]. Further, some patients have expressed concern about risk of arthritic disease in offspring, which may contribute to reduced fertility rates [25], and two previous studies have reported that women with RA and JIA sometimes are advised against having offspring [12, 25].

Previous population-based studies have reported an overrepresentation of various gynaecological disorders and surgery of the genital tract in women with rheumatic diseases [26, 27], which could also contribute to a higher proportion of nulliparity. In the present study, we did not have data of associated gynaecological disorders, and we did not know how many of the nulliparous women had tried to become pregnant. We also lacked information about use of contraceptives among patients

and references. In the present study, all patients were using DMARDs. Since many DMARDs are incompatible with pregnancy, the patients are advised to use contraceptives regularly.

RA, OCA and JIA women had significantly lower relative fertility rates after diagnosis (Table 2). The results are in accordance with two previous studies [5, 28]. One possible contributing factor to the reduced fertility rates may be the heavy disease burden of the study population. JIA women in the study were probably even more highly selected. Adult JIA patients treated with synthetic and/or biological DMARDs constitute ~50% of all patients diagnosed in childhood, and many of them have or will develop polyarticular disease [29].

Several studies of women with CIA have reported an increased frequency of Caesarean section (CS) compared with references [10, 14, 30–34]. Unpublished data from the present patient population have also shown an increased risk of CS among the patients compared with references (data under review). A Norwegian study has reported that a woman with CS as her first delivery will have fewer children than a woman who starts with a vaginal birth [35]. This may also contribute to the observed reduced number of children in the patient group.

Overall, we observed that the mean number of children was associated with age at the time of CIA diagnosis (Fig. 1), which is in accordance with previous reports of RA [5, 28]. Women diagnosed after 30 years of age had a mean number of children comparable to the reference group.

We did not observe any differences in the relative fertility rates in RA and OCA women vs references before disease onset (Table 2). Our finding contrasts with a previous publication where a lower fertility rate was reported prior to disease onset in RA, and especially a lower fertility rate was concentrated in an RF-positive subgroup of patients [6]. We did not examine RF-positive subgroups due to small numbers. Especially, the proportion of RF-positive patients was low in the OCA group.

We observed an increased inter-pregnancy interval for RA and OCA women diagnosed between first and second births. The increased interval indicates that women diagnosed after first birth may postpone a second pregnancy until the disease is better controlled. To our knowledge no other studies have reported this interval specifically before. No differences in inter-pregnancy intervals were observed for women with first and second births after diagnosis (Table 3). This contrasts with another study reporting an increased interval after diagnosis [28]. The different findings may be explained by improved treatment options during the last decade giving better disease control and opportunities to continue to a second pregnancy. Further, our findings indicate that women giving birth after diagnosis have their children within a shorter time frame. RA women with their first birth after diagnosis were older than references at the time of first delivery, and had less time left of their reproductive age (Table 3).

A strength of the present study was the use of references randomly selected from the general population. Some previous studies have used controls, which might bias the results (i.e. friends, newspaper advertisements or controls living in the same geographical area as the patients). We did not have information about educational level of the references, which is a limitation of the study, but we did not observe significant differences in educational level between nulliparous and parous patients for any of the diagnostic groups (results not shown).

Starting a family is of central importance in many people's lives, and also in CIA patients [25]. More knowledge around different aspects of fertility, both physical and psychological, is necessary to counsel CIA patients in this regard. After the introduction of biological DMARDs, clinicians are frequently asked about fertility aspects of CIA. Improvements in the medical treatment of arthritides may not immediately lead to increased fertility rates, but future studies of fertility rates will be of interest, including factors taking personal childbearing choices into account.

We summarize that a higher proportion of CIA women treated with DMARDs were childless compared with references. Reduced relative fertility rates were observed for all diagnostic groups, which add to the burden of CIA in general.

Rheumatology key messages

- A higher proportion of women with CIAs were childless compared with birth-year-matched references.
- Relative fertility rates were reduced in women with RA, OCA and JIA compared with references.

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