Number of Births, Interpregnancy Interval, and Subsequent Pregnancy Rate After a Diagnosis of Inflammatory Rheumatic Disease in Norwegian Women

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ABSTRACT. ***Objective.*** To study female reproduction, i.e., number of births, subsequent pregnancy rate, and interpregnancy interval after diagnosis of inflammatory rheumatic disease.

Methods. In a national population based cohort study, reproduction in mothers with rheumatic disease, registered with the Medical Birth Registry of Norway 1967–1995, were compared to mothers without such diagnoses.

Results. After diagnosis, women with rheumatic disease had a statistically significant lower mean number of births, a shorter time span of reproduction, longer interpregnancy intervals, and a reduced subsequent pregnancy rate.

Conclusion. Altered reproduction observed in women with a rheumatic disease might reflect various mechanisms not accounted for in this study, but possibly related to the disease process, functional impairment, or medical treatment. (J Rheumatol 2001;28:2310–4)

Key Indexing Terms:
REPRODUCTION
SUBSEQUENT PREGNANCY RATE
NATIONAL REGISTRY
INTERPREGNANCY INTERVAL
INFLAMMATORY RHEUMATIC DISEASE
NUMBER OF BIRTHS

Chronic inflammatory or systemic rheumatic diseases may have an influence on reproduction. Some of the mechanisms involved may relate to pathophysiological aspects; others may result from an active wish to limit family size. Most women with rheumatic disease want children[1] and are likely to contact a doctor when they consider reproduction. At our Center for Mothers with Rheumatic Disease, connected with the Department of Rheumatology, problems due to reduced fertility have been more frequently addressed during the last 5 years, triggering our interest to study reproduction related to the diseases. Except for 2 population based studies of female patients with rheumatoid arthritis (RA) showing significantly reduced fecundity and fertility, respectively[2,3], and one population based study of female patients with systemic lupus erythematosus (SLE)[4], most previous studies have included a low number of patients and might have been biased by selection.

In a cross sectional population based study in women ages 40–42 years with self-reported rheumatic disease in Middle-Norway, we found no difference between patients and controls regarding the mean number of children, mean maternal age at first and last live birth, mean interpregnancy interval, and other variables of reproduction[5]. A large separate database, the Medical Birth Registry of Norway (MBRN) that comprises data on all births from 1967[6], was utilized to assess to what extent these results were representative and to further clarify controversial aspects of reproduction in women with rheumatic disease.

MATERIALS AND METHODS

Medical Birth Registry of Norway. Established in 1967, the MBRN is based on compulsory notification of all births after 16 weeks of gestation and comprises data relevant to epidemiological studies of health problems among pregnant women and infants[6]. In a notification form unchanged 1967 to 1995, data on demographic variables, pregnancy, maternal disease, delivery, and the newborn have been reported by the attending midwife and doctor. Maternal disease was coded by the international classification of diseases (ICD8). Medication was not included.

Patients and references. We analyzed data for all single births in Norway in 1967 to 1995. By the mother's national identification number all births were linked into sibships, which were used as the unit of analysis. Sibships with multiple births and sibships in which the first birth occurred before 1967 were excluded. Patients were defined as all women noted to have a rheumatic disease before the first birth (n = 1933); all other women formed the reference group (n = 672,691). The total number of infants in patients with rheumatic disease was 3325 and in the reference group 1,396,180. Due to the small number of patients with rare rheumatic diseases, all diseases were grouped into 3

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categories according to the ICD8: (1) connective tissue diseases (CTD) (ICD8: 734 and 716: SLE, systemic sclerosis, Sjögren's syndrome, and polymyositis/dermatomyositis); (2) specified inflammatory arthritides (SA) (ICD8: 712: RA, juvenile rheumatoid arthritis, ankylosing spondylitis); and (3) nonspecified inflammatory arthritides (NSA) (ICD8: 715).

Epidemiological measures. The subsequent pregnancy rate was defined as the percentage of all women (cases as well as references) who continued from the first birth (birth order one) to a second birth (birth order two). 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 pregnancy (birth) and was given in terms of median years. Infant survival was defined as the proportion of all births after 16 weeks of gestation surviving the first year of life. Time periods 1967–76, 1977–86, and 1987–95 were established for some of the analyses.

Statistical analyses. Differences between disease groups and references regarding mean number of births and mean maternal age at first and last birth were tested by separate analysis of variance. Analyses of mean number of births and maternal age at last birth were adjusted for infant survival and maternal age at first birth. Due to a higher proportion of women with rheumatic disease diagnosed in the last time period (CTD 73.1%, SA 59%) and the possibility of births after the end of study (December 31, 1995), additional analyses of the number of births and maternal age at last birth were done with restriction applying only to women who had at least 10 years of followup after a birth.

Interpregnancy intervals and subsequent pregnancy rate were estimated by Cox proportional hazards analysis[7], adjusted for maternal age at first birth and infant survival, and due to an interaction between time period and rheumatic disease, specified for each time period. The median interpregnancy interval was calculated by Kaplan-Meier analysis. Women who did not have a subsequent pregnancy (second birth) were treated as censored observations with censored time equal to the last date of registration (December 31, 1995) or at the age of 50. The assumption of proportional hazards was assessed by log-minus-log survival plots[8]. Estimates from Cox analysis were used to calculate adjusted survival curves at mean values of the risk factors. The analyses were performed with the statistical package SPSS 10.0 (1999) for Windows.

RESULTS

Except for women with nonspecified inflammatory arthritides, women with rheumatic disease had a statistically significant lower mean number of children than the reference group (Figure 1), an observation also made in all 3 time periods 1967–76, 1977–86, 1987–95 (data not shown). This was most obvious in the group with CTD [mean 1.7, 95% confidence interval (CI): 1.5–1.9]. Analyses restricted to sibships with an observation period of at least 10 years after the last birth did not change the result. Women with rheumatic disease had a statistically significant higher mean age at first birth and lower mean age at last birth compared to references (Table 1). Thus, the period of reproduction was shorter in women with rheumatic disease. The results remained the same when the analysis was restricted to 10 years of followup after last birth.

Women with a rheumatic disease diagnosed before the first birth had a statistically significant reduced subsequent pregnancy rate compared to references, and this reduction was greatest in women with CTD, but in the last time period the subsequent pregnancy rate of women with CTD did not differ from references. A significant interaction was found with the time period, implying increased subsequent pregnancy rates in the disease groups with time (p = 0.006) (Table 2, Figure 2). The median interpregnancy interval (applying to all women)

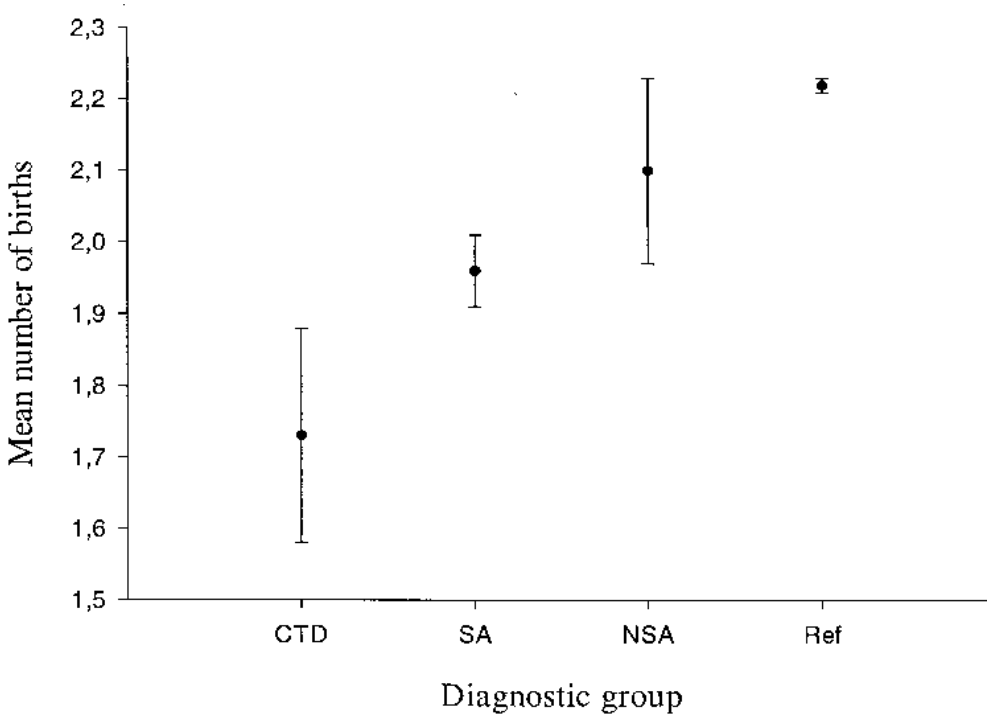

Figure 1. Mean number of births, adjusted for maternal age at first birth and infant survival, with 95% CI in mothers with rheumatic disease diagnosed before the first birth and in references who had one or more births, Norway, 1967–95.

Table 1. Mean age at first and last birth in women with rheumatic disease diagnosed before the first birth and in the reference group, Norway, 1967–95.

	Total N	Maternal Age at First Birth, yrs Mean	95% CI	Maternal Age at Last Birth*, yrs Mean	95% CI
Diagnostic group					
CTD	134	26.6	25.8–27.3	29.4	28.7–30.1
SA	1642	25.7	25.5–25.9	30.0	29.8–30.2
NSA	157	25.1	24.4–25.8	30.6	30.0–31.2
References	672,691	23.8	23.8–23.8	30.8	30.8–30.9

* Adjusted for maternal age at first birth and infant survival.
CTD: connective tissue disease, SA: specified inflammatory arthritides, NSA: nonspecified inflammatory arthritides.

Table 2. Subsequent pregnancy rate after the first birth and median interpregnancy interval (applying to all women) from the first to the second birth in women with rheumatic disease diagnosed before the first birth, and in the reference group, Norway, 1967–95.

Period	Diagnostic Group	Total N	Subsequent Pregnancy N	%	RR*	95% CI	Median** Yrs	95% CI
1967–76	CTD	10	3	30.0	0.22	0.07–0.69	***	
	SA	166	113	68.1	0.67	0.56–0.81	3.4	2.7–4.1
	NSA	64	41	64.1	0.56	0.41–0.76	4.1	3.5–4.8
	Ref	243,553	206,773	84.9	1.00		2.7	2.6–2.7
1977–86	CTD	25	14	56.0	0.53	0.31–0.89	4.1	0.0–8.2
	SA	494	368	74.5	0.86	0.78–0.96	3.5	3.1–3.9
	NSA	61	40	65.6	0.73	0.53–0.99	3.9	2.3–5.4
	Ref	206,276	169,149	82.0	1.00		3.1	3.0–3.1
1987–95	CTD	93	40	40.0	0.82	0.60–1.12	4.0	2.4–5.6
	SA	957	411	43.0	0.85	0.77–0.94	3.8	3.4–4.3
	NSA	29	15	51.7	0.79	0.48–1.31	4.7	1.3–8.2
	Ref	215,885	104,116	48.2	1.00		3.2	3.2–3.2

* Subsequent pregnancy rate ratios (RR) estimated by Cox regression model with adjustment for maternal age at first birth and infant survival. ** Median interpregnancy years and 95% CI estimated by Kaplan-Meier analysis. *** Only 30% continued to a second birth (after 3.3 yrs).

was longer in women with rheumatic disease compared to references (Table 2, Figure 2). There was a significant increase in median interpregnancy interval in cases of specified inflammatory arthritides in all time periods compared to references. Five years after the first birth 56.7% (95% CI 46.4–67.0) of CTD women, 61.6% (95% CI 58.9–64.4) of SA women, and 57.1% (95% CI 49.2–65.1) of NSA women had their second birth compared to 69.1% (95% CI 68.0–70.3) of references (total period 1967–95).

DISCUSSION

In this first population based, national study assessing the reproductive pattern in women with rheumatic disease, we found a statistically significant lower mean number of births and a reduced period of reproduction compared to references. In patients with CTD, a higher risk of miscarriage before 16 weeks of gestation might contribute to the lower number of children[9,10]. However, our study did not include data on first trimester pregnancy loss. Previous studies of SLE and systemic sclerosis have reported slightly reduced numbers of births in patients compared to controls[4,11]. A prospective study of planned SLE pregnancies found no difference in the birth rate in patients with SLE compared to the normal population[12]. Except for one population based retrospective study[3] and 2 other studies of RA women[13,14], no other studies of patients with RA have found a statistically significant reduction in number of births[2,15-17]. The discrepancy between our present and previous results may partly be due to a different study design. Our study was population based and included the total cohort of mothers giving birth between 1967 and 1995, whereas several other studies have had small sample sizes and also selection biases in both cases (only cases who plan a pregnancy) and controls (friends, relatives, neighborhood, newspaper advertising), which may reduce or increase potential differences between cases and controls.

Similarly, we found an increased interpregnancy interval and a reduced subsequent pregnancy rate in women with rheumatic disease. A secular trend was observed with an increasing subsequent pregnancy rate from the first to the last time period. This finding may indicate better monitoring and

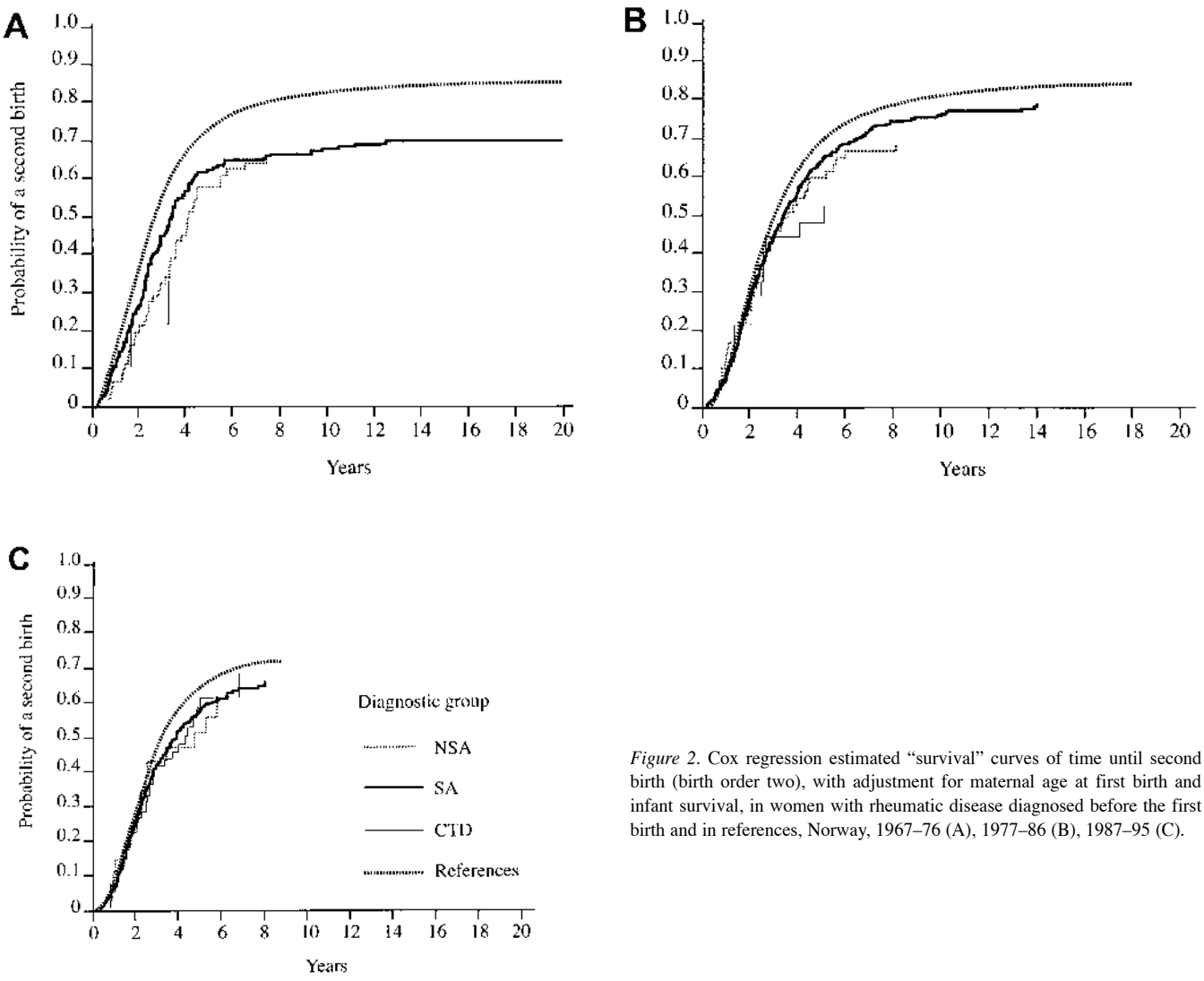

Figure 2. Cox regression estimated "survival" curves of time until second birth (birth order two), with adjustment for maternal age at first birth and infant survival, in women with rheumatic disease diagnosed before the first birth and in references, Norway, 1967–76 (A), 1977–86 (B), 1987–95 (C).

treatment of women with rheumatic disease in the last decades and improvement in dealing with high risk pregnancies. In a study of healthy women, the most important factors influencing the interpregnancy interval were the outcome of the previous pregnancy, social class, and maternal age[18]. In our study, the interpregnancy interval was significantly increased in women with rheumatic disease independent of maternal age. It is less likely that social class or cultural differences have influenced our results. The Norwegian population comprises 95% Caucasians and is socioeconomically a rather homogeneous population. The country has a public health care and social security system covering all citizens that is particularly beneficial for families with small children. Loss of income due to disease is nearly completely compensated for by social security. Previously, we reported a higher perinatal and postperinatal mortality in births of women with rheumatic disease[19]. When the subsequent pregnancy rate was adjusted for infant survival, it remained significantly decreased. Few studies have addressed interpregnancy interval time in women with rheumatic disease[5], but one study has found an increased interval to conception in RA cases prior to the first, second, and third pregnancies[3].

A number of factors may cause an increased interpregnancy interval and a reduced reproductive period. Miscarriage before 16 weeks of gestation may cause increased interpregnancy interval. Negative pregnancy or postpartum experience can reduce the wish for a subsequent child. However, rheumatic disease may also reduce the ability to conceive (reduced fecundity) either by hormonal disturbances induced by the disease process or medications applied[20,21]. Also, a significantly reduced fecundity in RA patients before disease onset has been reported[2]. Some antirheumatic drugs are not compatible with pregnancy (e.g., cytotoxics) and some can disturb ovulation (e.g., nonsteroidal antiinflammatory

drugs[22]). Unfortunately, drug data are not available in the MBRN. Another factor influencing family size is the frequency of intercourse, which has been found reduced in patients with rheumatic disease and may be caused by impaired function and lessened sexual desire[23].

The prevalence of the rheumatic diseases in this study fits with the prevalence rates of rheumatic diseases of fertile women in other Scandinavian studies[24-27]. In a smaller sample a validity test of the diagnosis of rheumatic disease in the MBRN was performed by linking a local database (with verified diagnoses) to the MBRN by means of the patient identification number. Thus, 93% of births in women having a diagnosis of rheumatic disease in the MBRN had a correct diagnosis (unpublished data). Possible misclassification of rheumatic disease may have been greatest in the first time period due to lack of good diagnostic criteria and diagnostic tools consistent with the reduction in the proportion of women with nonspecified arthritides from the first to the last time period of the study[28].

Although women with rheumatic disease do wish for children[1], our study indicates these women have a reduced family size. Many factors may be involved and vary from one patient to another. To improve counselling, further studies of possible factors involved are necessary.

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