Miscarriage and Stillbirth in Women with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To examine the risk of pregnancy loss in women with rheumatoid arthritis (RA).

Methods. Cumulative numbers of early miscarriages (before gestational Week 12), late miscarriages (weeks 12–22), and stillbirths reported to the Medical Birth Registry of Norway in the period 1999–2009.

Results. There were 1578 women with RA and 411,130 reference women included in the study. Relative risks of early and late miscarriage in women with RA versus references were 1.2 (95% CI 1.1–1.3) and 1.4 (95% CI 1.1–1.7), respectively. There was no difference in stillbirth.

Conclusion. The risk of miscarriage was slightly higher among women with RA than in references.

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RHEUMATOID ARTHRITIS SPONTANEOUS ABORTION STILLBIRTH
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Spontaneous abortion (SA) is the most frequent disorder of human pregnancy, affecting around 12% of first-trimester pregnancies[1]. Early miscarriage before Week 12 of pregnancy is often not diagnosed or reported. Late miscarriage between 12 and 22 weeks of gestation complicates less than 1% of pregnancies[1]. Women with rheumatoid arthritis (RA) planning a pregnancy often ask if they have an increased risk of SA, and the answer is not straightforward. Three previous studies have indicated no increased risk of SA in women with RA compared with women not diagnosed with any inflammatory rheumatic disease[2,3,4]. Only a few reports on miscarriage in RA have been published since 2000[2,5]. Stillbirth has been sparsely examined in women diagnosed with RA. Two studies reported no increased risk of stillbirth[4,6]. New studies of risks of SA and stillbirth are necessary because new treatment options such as biologic agents and the treat-to-target principle may have changed the RA population[7].

The aim of our present study was to examine the risk of SA and stillbirth in women diagnosed with RA.

MATERIAL AND METHODS

Setting. The national Medical Birth Registry of Norway (MBRN) was established in 1967[8]. From December 1, 1998, a revised notification form was introduced that included registrations of SA, live births, and stillbirths from gestational Week 12. The notification form was completed by the attending midwife at the end of each pregnancy, cosigned by the attending physician, and received at the MBRN within 1 week after delivery. Information in the form was on 3 elements: (1) a standardized national form used during pregnancy by the patient's physician, (2) oral information given by the patient when admitted to the hospital, and (3) information from the doctor and the midwife about the actual delivery and the newborn. For each registration in the MBRN, the women were also asked about the number of previous SA before gestational Week 12. Based on the unique identification number for each mother, the MBRN provided records in which consecutive birth records for the same mother were linked. From these files, we extracted information on all occurrences of late SA, live births, and stillbirths for each mother. The cumulative number of early SA reported by the woman was extracted from her last delivery record. Women not reporting information were included, assuming they had no early SA.

After December 1, 1998, all women diagnosed with RA were registered in the MBRN by specific coding according to the International Classification of Diseases (ICD)-10 systems. The diagnosis is based on information from the patient's physician and information in the patient records at the hospital. In our present study, we included data from women registered with RA from their first registration in the MBRN in the period between December 1, 1998, and December 31, 2009.

The study was carried out in compliance with the Helsinki Declaration

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Patients and references. Women registered with RA (ICD-10 codes M05.0, M05.1, M05.2, M05.8, M05.9, M06.0, M06.8, and M06.9) were compared with references (all other births in the MBRN dated between December 1, 1998, and December 31, 2009 in which the mother did not have any registrations of inflammatory rheumatic disease). We excluded maternal diagnoses of inflammatory connective tissue diseases, other inflammatory joint diseases, and vasculitis, as listed in Appendix 1. The excluded diagnoses constituted around 3200 births out of the total of about 565,000 births during the study period.

Outcomes. We used maternal age and parity at last delivery and information on previous early SA before gestational Week 12, late SA from Week 13 until Week 22, and stillbirths from gestational Week 22 onward.

Analyses. Group comparisons were performed with the Student t test for continuous variables and the chi-square test for categorical variables. Poisson regression analysis was applied to estimate relative risks (RR) with corresponding 95% CI of previous SA and stillbirths in women with RA versus references, and with adjustments for parity and maternal age at the time for reporting of events (last delivery). P values < 0.05 were considered significant. Data were analyzed using the Statistics/Data Analysis (STATA), version 12.1 (Stata Corp) and the Statistical Package of Social Sciences, version 21.0 (SPSS Inc.).

RESULTS

Overall, 10% of both women with RA and references had not reported information about previous early SA. Significantly more women with RA than reference women reported at least 1 early or late SA (Table 1). RR of early and late SA were significantly higher among women with RA than references (Table 2). Among women with RA reporting early SA, 12% had 3 or more events versus 8% in references (p = 0.007). For late SA, 6% of women with RA reported 3 or more events versus 4% among references (p = 0.4). There was no significant difference in the risk of stillbirth (Table 2).

DISCUSSION

In the present retrospective epidemiological study, the prevalence of at least 1 event of early or late SA was higher among women with RA than in women from the general population. Women with RA also had a significantly higher risk of SA, both early and late. The risk of stillbirth was similar between the groups. Recurrent events of early SA were also more frequent in the RA group. This indicates that women with RA experience SA more often compared with women from the general population. We observed a mean number of around 0.5 SA per woman with RA, which is in accordance with another study, but the other study did not have a comparison with the general population[6]. Although we found a statistically significant difference between women with RA and women in the general population, the clinical significance of the observed difference is probably small.

Our results are in contrast to 1 retrospective population-based study from 2006 reporting no difference in the risk of SA between women with RA and references[2]. This particular study included 183 parous women with RA and 1076 parous controls. We do not see a clear reason for the conflicting results between the studies, but the previous study may have been underpowered to demonstrate a true risk difference. Three previous studies published between the periods 1986 to 1990 were small and not population-based, and they did not distinguish between early and late SA[3,4,9]. One of these studies including 96 women with RA reported a higher risk of SA among patients[9].

A strength of our study was the access to the data of all births within Norway within the study period, thus limiting the selection bias of patients and securing the access to reference women from the general population.

Our study has limitations. The study only included SA in parous women because we used data from a birth registry. Among all included women, 10% did not report information about previous early SA, but these women were included in the analyses, assuming that they had no SA because some women did not report negative answers. This may introduce a misclassification bias toward the null and dilute a "true" association.

Further, we did not have information about administration of medication at time of conception. Administration of methotrexate (MTX) at the time of conception has been associated with an increased risk of SA[10]. In a Swiss study, 20% of pregnancies in women with arthritis occurred under treatment with disease-modifying antirheumatic drugs (DMARD) such as MTX at the time of conception[11]. Women taking MTX would also be more likely to terminate pregnancy because of the teratogenic risk associated with MTX exposure[11]. We did not have information about elective abortions in our study. Use of DMARD or planning of pregnancy might present women with RA for prenatal care earlier in gestation than the rest of the population. This could lead to an erroneously higher rate of reported early SA in women with RA because the pregnancies might be recognized earlier than in the general population.

Two population-based studies have indicated an association between the use of nonsteroidal antiinflammatory drugs and SA[12,13]. However, the results of these studies have been debated because they examined prescribed medication and not actual use. In one of the studies, a subanalysis of women with RA did not show any association with SA[12].

Table 1. Proportion of women with RA and women from the general population reporting the events of SA and stillbirths, and characteristics of the women. Values are frequency (%) unless otherwise specified.

Characteristics	Women with RA, n = 1578	Reference Women, n = 411,130	p*
Age at time of last delivery, yrs, mean (SD)	32.1 (4.8)	30.9 (5.1)	< 0.001
Parity, mean (SD)	2.3 (2.1)	2.1 (2.0)	< 0.001
Early SA, < Week 12	413 (26.2)	88,697 (21.6)	< 0.001
Late SA, weeks 12–22	71 (4.5)	14,539 (3.5)	0.04
Stillbirth, ≥ Week 22	20 (1.3)	4522 (1.1)	0.34

* Student t test or chi-square test. RA: rheumatoid arthritis; SA: spontaneous abortion.

Table 2. Mean number of SA and stillbirths and the relative risk of SA and stillbirth in women with RA versus reference women from the general population. Values are given as mean (SD) range unless otherwise specified.

Variables	Women with RA, n = 1578	Reference Women, n = 411,130	RR	95 % CI	p*
Early SA, < Week 12	0.46 (0.91) 0–9	0.34 (0.75) 0–20	1.3†	1.1–1.4	< 0.001
			1.2‡	1.1–1.3	< 0.001
Late SA, weeks 12–22	0.07 (0.36) 0–6	0.05 (0.31) 0–21	1.3†	1.01–1.6	0.04
			1.4‡	1.1–1.7	0.002
Stillbirth, ≥ Week 22	0.02 (0.15) 0–3	0.01 (0.12) 0–8	1.2†	0.8–1.9	0.34
			1.3‡	0.9–1.9	0.19

* Poisson regression analysis and Student t test. † Crude values. ‡ Adjusted for parity and maternal age at last delivery. RA: rheumatoid arthritis; SA: spontaneous abortion; RR: relative risk.

Another limitation was that no validation study of RA diagnoses in the MBRN exists. However, a validation study of a selection of diagnoses of inflammatory rheumatic disease in the MBRN reported that 97% of the diagnoses were correct with respect to the type of rheumatic disease[14]. Since around 1995, Norwegian guidelines for the monitoring of pregnant women with inflammatory rheumatic diseases have existed and therefore the doctors involved are well informed about the diagnosis.

Another limitation was the possibility of recall bias in reporting SA, but this bias was probably equal among women with RA and reference women. We used records in which consecutive birth records to the same mother were linked. A previous study found that reproductive history based on such records were of better quality than routinely collected data based on maternal recall[15]. We did not have information about the time of SA, time of diagnosis of RA, socio-economic status, or smoking habits at the time of SA.

In this retrospective study based on national data, we observed a slightly higher risk of SA among women with RA compared with women from the general population.

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APPENDIX 1. Excluded International Classification of Diseases, 10 ed. codes from the patient and reference groups were systemic lupus erythematosus (M32.1, M32.8, M32.9), Sjögren syndrome (M35.0), mixed connective tissue disease (M35.1), systemic sclerosis (M34.0, M34.1, M34.2, M34.8, M34.9), poly/dermatomyositis (M33.0, M33.1, M33.2, M33.9), other specified connective tissue disease (M35.8), unspecified connective tissue disease (M35.9), Still disease (M06.1), ankylosing spondylitis/spondyloarthritis (M45, M46.0, M46.1, M46.8, M46.9), psoriatic arthritis (M07.0, M07.1, M07.2, M07.3; +L40.5 for all diagnoses), juvenile idiopathic arthritis (M08.0, M08.1, M08.2, M08.3, M08.4, M08.8, M08.9), unspecified arthritis (M13.0, M13.1, M13.8, M13.9), polyarteritis nodosa (M30.0), granulomatosis with polyangiitis (M31.3), Takayasu arteritis (M31.4), microscopic polyangiitis (M31.7), and Behçet disease (M35.2). In addition, rheumatoid arthritis (M05.0, M05.1, M05.2, M05.8, M05.9, M06.0, M06.8, M06.9) was also excluded from the reference group.