

# Breastfeeding among Women with Rheumatoid Arthritis Compared with the General Population: Results from a Nationwide Prospective Cohort Study

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**ABSTRACT. Objective.** The World Health Organization recommends that infants be exclusively breastfed until the age of 6 months. The first objective was to compare breastfeeding frequencies and time of cessation between women with rheumatoid arthritis (RA) and the general population. The second objective was to identify why patients with RA discontinue breastfeeding.

**Methods.** This study was embedded in the Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study, a nationwide prospective cohort study. From 2002 to 2008, a total of 249 pregnancies were followed from pregnancy until 6 months postpartum. Data on lactation and medication use were collected. Proportion tests were used to compare percentages of breastfeeding between the study population and the general/reference population.

**Results.** At 4–6, 12, and 26 weeks postpartum, 43%, 26%, and 9% of the RA patients breastfed their offspring, respectively, compared with 63%, 46%, and 41% in the general population, respectively ( $p < 0.001$ ). The main reason for women to discontinue breastfeeding was the restart of medication ( $n = 129$ , 57.8%). Nevertheless, more than 40% of these patients restarted medication that was considered compatible with breastfeeding.

**Conclusion.** This large prospective study demonstrates that RA is associated with lower proportions of women breastfeeding their offspring and earlier cessation compared with the general population. A considerable number of patients discontinued breastfeeding so that they could start medication, even though many of the medications are considered safe to use during lactation. Using the results of this study, intervention strategies supporting RA patients who wish to breastfeed may be developed. (J Rheumatol First Release May 1 2019; doi:10.3899/jrheum.180805)

*Key Indexing Terms:*

BREASTFEEDING RHEUMATOID ARTHRITIS PREGNANCY MEDICATION

Research on the effect of pregnancy on rheumatoid arthritis (RA) and the consequences of RA on pregnancy has gained interest in recent years. However, breastfeeding in patients with RA is a neglected area; there are few studies on this subject. There are no studies available that compare breastfeeding frequency and duration in RA with the general population. Considering lactation in patients with RA, one prospective study that focused on disease activity in relation with breastfeeding showed worse disease activity 6 months postpartum in first-time breastfeeding women compared with non-breastfeeding women<sup>1</sup>.

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The World Health Organization recommends to exclusively breastfeed infants until the age of 6 months, and to continue breastfeeding until 2 years (or beyond) alongside complementary foods<sup>2</sup>. Besides being the most optimal infant nutrition and improving the bond between mother and child<sup>3,4</sup>, breastmilk also benefits longterm health<sup>2,5,6,7,8,9,10</sup>. Breastfeeding has especially significant benefits for high-risk infants born prematurely<sup>5</sup>. Because RA may harm pregnancy outcomes<sup>11</sup>, breastfeeding might be of utmost importance for the offspring of patients with RA.

In view of the increased risk of a flare of RA within 3 months postpartum, medication is often restarted after delivery<sup>12</sup>. Safety data on the use of most antirheumatic drugs during lactation are absent or limited<sup>13</sup>. At the time we conducted this study, medications that were considered safe during lactation were conventional disease-modifying antirheumatic drugs such as hydroxychloroquine (HCQ), sulfasalazine (SSZ), and antiinflammatory drugs such as prednisone and nonselective nonsteroidal antiinflammatory drugs (NSAID)<sup>14</sup>. Drugs that were advised to be avoided during lactation included methotrexate (MTX) and leflunomide (LEF). Also not recommended to be prescribed

during lactation were biologicals, all selective cyclooxygenase-2 inhibitors, and azathioprine (at the time this study was conducted)<sup>14</sup>.

The aims of the current prospective study were first to compare frequency and duration of breastfeeding in women with RA with the general population; second, to identify reasons why RA patients discontinue breastfeeding; and finally, to identify clinical factors in the third trimester of pregnancy associated with discontinuation of breastfeeding within 3 months postpartum. This study will help to understand the effect of RA on lactation, and to develop intervention strategies to support RA patients who wish to breastfeed.

## MATERIALS AND METHODS

**Study population.** The study cohort consisted of women who participated in the Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study, a nationwide prospective cohort study from the Netherlands with an inclusion period from 2002 to 2008 (last visit in 2010), described in detail previously<sup>15</sup>. Patients were recruited by their rheumatologist if they met the American College of Rheumatology 1987 revised criteria for RA<sup>16</sup>. Inclusion was possible if patients had a wish to conceive, or when they were already pregnant (preferably in the first trimester). In total, 249 pregnancies were available for the current analysis<sup>17</sup>.

The reference group consisted of 3009 women recruited throughout the Netherlands in 2005 for a population-based study on breastfeeding, representative of the general population at that time<sup>18</sup>. Women were eligible for inclusion if their infant was aged 6 months or younger.

**Data collection.** In the PARA study, patients were visited by a research nurse at home before pregnancy, 3 times during pregnancy, and 3 times postpartum (6, 12, and 26 weeks). At all timepoints a physical examination was performed and information on the mother (e.g., disease activity, functionality, medication) and child was collected. Postpartum data on child feeding were collected using questionnaires. These included questions on the start and duration of breastfeeding, on exclusive breastfeeding or combined with infant formula, or on exclusive formula, and on the reason for discontinuing breastfeeding (restart of medication, maternal/child-related reasons, or a combination). Maternal reasons were the following: no desire to, mastitis, work, too much effort, not enough milk, and breast surgery. Child-related reasons were difficulty in latching, failure to thrive, and illness.

The Disease Activity Score based upon 3 variables, swelling and tenderness in 28 joints and C-reactive protein 3 (DAS28-CRP3), was used to measure disease activity<sup>19,20</sup>. Remission was defined as DAS28-CRP3 < 2.6, and low disease activity as  $\geq 2.6$  < 3.2<sup>15</sup>. In 10 patients, the DAS28-CRP3 in the third trimester was missing. Because the correlation between DAS28-CRP3 in the second and third trimesters was high (0.7), it was substituted with the DAS28-CRP3 from the second trimester in these patients.

As a measure for functionality, the conventional Health Assessment Questionnaire (HAQ) score was determined using the validated Dutch translation of the Stanford HAQ, which considers the use of devices and aids<sup>20,21,22</sup>. Rheumatoid factor (RF) and anticitrullinated protein antibody (ACPA) were measured in the third trimester.

In the reference group, questionnaires were used to determine, among others, frequency and duration of breastfeeding, whether breastfeeding was exclusive or combined with infant formula, or whether infant formula was used exclusively.

**Statistical analysis.** Descriptive statistics were calculated as numbers, percentages, means, medians, SD scores, and interquartile ranges (IQR). Proportion tests were used to compare percentages of breastfeeding between the study population and general/reference population. Chi-square tests were

used to compare frequencies between groups. Student t tests were used to compare DAS28-CRP3 between breastfeeding and non-breastfeeding patients.

Subgroups based on birth weight were created (birth weight < 2500 g and  $\geq 2500$  g). Chi-square tests were used to compare breastfeeding frequencies between low and normal birth weight infants.

For the analysis of early cessation of breastfeeding, a multivariable logistic regression model was built. Covariables with  $p < 0.2$  in univariable analysis were used in the multivariable model. After that, the model was fitted step-by-step using backward selection of variables with  $p > 0.2$ . The dependent variable was discontinuation of breastfeeding before 12 weeks postpartum. Independent variables were the HAQ in the third trimester, the autoantibody status, use of MTX in the past, the socioeconomic status (SES) based on educational level, prednisone use in the third trimester, SSZ use in the third trimester, the presence of erosions, DAS28-CRP3 in the third trimester, maternal smoking periconceptionally and/or during pregnancy, the visual analog scale for global health in the third trimester, maternal age, and parity.

A subgroup analysis was performed including only the first participation of the patients in the PARA study. Breastfeeding frequencies were once again analyzed using chi-square tests, and the regression model was repeated in this group.

Statistical significance was defined as  $p \leq 0.05$ . All statistics were performed using Stata software version 15.1 for Windows.

**Ethics.** This study is in compliance with the Declaration of Helsinki. The Medical Ethics Committee at the Erasmus Medical Center Rotterdam, the Netherlands, approved the PARA study (MEC-214.320/2002/117). All participants provided written informed consent.

## RESULTS

**Participants.** In the PARA study, a total of 369 patients were included, which resulted in 256 successful pregnancies. The DAS28-CRP3 in the second and third trimesters were missing in 7 pregnancies. After exclusion of these, data on 249 pregnancies from 216 women were available for the current analysis. Descriptive statistics of the study population are shown in Table 1. The mean maternal age at delivery was 32.8 years and the median duration of RA was 4.9 years. The mean DAS28-CRP3 was 3.4 in the third trimester.

Since the median HAQ in the third trimester was 0.75 (IQR 0.25–1.25), the HAQ was dichotomized to lower (< 0.75) and higher ( $\geq 0.75$ ) HAQ. This resulted in 114 patients (45.8%) with lower, and 135 patients (54.2%) with higher HAQ.

In total, 186 patients (74.7%) were classified as RF- and/or ACPA-positive. About half of the patients had high SES based on educational level (universities of applied sciences and academic university education). In total, 22 patients (8.8%) smoked periconceptionally or during pregnancy.

**Breastfeeding.** In total (exclusive and partial breastfeeding combined), 108 patients (43%) breastfed their offspring until at least 4–6 weeks, 65 (26%) until at least 12 weeks, and 23 (9%) until at least 26 weeks postpartum compared with 63%, 46%, and 41%, respectively, in the reference population (all  $p < 0.001$ ; Table 2). In the PARA study, breastfeeding frequency and duration were not different between nulliparous and multiparous patients with RA.

Because breastmilk has particular benefits for infants with

Table 1. Descriptive statistics of study population.

| Baseline Characteristics                            | N = 249 Pregnancies |
|---|---------------------|
| Maternal age at delivery, mean (SD), yrs            | 32.8 (3.8)          |
| Duration RA at baseline, median (IQR), yrs          | 4.9 (2.2–9.8)       |
| DAS28, 3rd trimester, mean (SD)                     | 3.4 (1.1)           |
| DAS28-CRP, 3rd trimester <sup>#</sup>               |                     |
| < 2.6 (remission)                                   | 72 (28.9)           |
| ≥ 2.6 to < 3.2 (low disease activity)               | 43 (17.2)           |
| ≥ 3.2 to ≤ 5.1 (intermediate disease activity)      | 118 (47.4)          |
| > 5.1 (high disease activity)                       | 16 (6.4)            |
| HAQ, 3rd trimester, median (IQR)                    | 0.75 (0.25–1.25)    |
| Parity  |                     |
| Nulliparous (no previous offspring)                 | 124 (51.5)          |
| Multiparous (≥ 1 previous offspring)                | 117 (48.5)          |
| RA-associated autoantibodies                        |                     |
| Either RF- or ACPA-positive, or both positive       | 186 (74.7)          |
| Both negative                                       | 63 (25.3)           |
| RF-positive   | 172 (69.1)          |
| ACPA-positive                                       | 153 (61.5)          |
| Presence of erosions                                | 150 (60.2)          |
| Methotrexate use in the past                        | 143 (57.4)          |
| Biological agent use in the past                    | 44 (17.7)           |
| Medication use during 3rd trimester                 |                     |
| Prednisone only                                     | 63 (25.3)           |
| Sulfasalazine only                                  | 37 (14.9)           |
| Both prednisone and sulfasalazine                   | 22 (8.8)            |
| Hydroxychloroquine (either alone or in combination) | 4 (1.6)             |
| No medication during 3rd trimester                  | 123 (49.4)          |
| SES based on educational level                      |                     |
| Low   | 16 (6.4)            |
| Middle  | 79 (31.7)           |
| High  | 131 (52.6)          |
| Unknown   | 23 (9.2)            |
| Smoking <sup>§</sup>                                | 22 (8.8)            |

Values are n (%) unless indicated otherwise. Normally distributed data are presented as mean (SD); non-normally distributed data are presented as median (IQR). <sup>#</sup> Disease activity groups are defined according to the European League Against Rheumatism criteria. <sup>§</sup> Smoking periconceptional or during pregnancy. RA: rheumatoid arthritis; IQR: interquartile range; DAS28: 28-joint count Disease Activity Score; DAS28-CRP3: DAS28 using C-reactive protein levels; RF: rheumatoid factor; ACPA: anticitrullinated protein antibody; SES: socioeconomic status; HAQ: Health Assessment Questionnaire.

low birth weight<sup>5</sup>, subgroups based on birth weight were created in the offspring born to women with RA from the PARA study, resulting in 23 infants with a birth weight

< 2500 g and 226 with a birth weight ≥ 2500 g. Only 26.1%, 17.4%, and 4.4% of the offspring < 2500 g were breastfed at 4–6 weeks, 12 weeks, and 26 weeks, respectively, compared with 45.1%, 27.0%, and 9.7%, respectively, in offspring with a birth weight ≥ 2500 g (not significant).

In total, 33 women participated more than once in this study. To exclude possible selection bias in the obtained results, a subgroup analysis including only the first participation of the patients (n = 216) was performed. Similar results in breastfeeding frequency and duration were obtained (data not shown).

**Reasons for discontinuation.** In total, 223 patients discontinued breastfeeding over the course of 26 weeks. In 129 patients (57.8%), the reason for discontinuation of breastfeeding was restart of medication (Table 3). Of these 129 patients, 86 (61.0%) reported that the reason for cessation was restart of medication before 6 weeks, 28 patients (65.1%) between 6–12 weeks, and 15 patients (38.5%) between 12–26 weeks postpartum. In 76/129 patients (58.9%), medication that was considered incompatible with lactation (at the time this study was conducted) was initiated. The other 53 patients (41.1%) received (a combination of) prednisone (49.1%), SSZ (39.6%), HCQ (18.9%), and/or nonselective NSAID (37.7%), all considered safe to use during lactation.

In total, 94 patients (42.2%) reported reasons for cessation other than restart of medication. Of these, the majority (n = 77, 81.9%) included maternal reasons, for example, “not enough milk” (35.1%) and “no desire to” (17.0%). As for child-related reasons (n = 15, 16.0%), the majority included “struggle to latch” (7.4%) and “failure to thrive” (6.4%; Table 3). In the general population (the Netherlands 2000–2003<sup>23</sup>), cessation owing to “not enough milk” (including concern about the amount of milk), “problems relating to breasts and/or nipples,” and “health problems in the infant” were comparable with the results from this study. Work-related cessation was reported in 7.4% of the patients in our study (in patients with reasons other than restart of medication) compared with 13.9% in the general population (p < 0.05)<sup>23</sup>.

As for the subgroups based on birth weight, about half of the patients with an offspring < 2500 g reported discontinuation due to maternal reasons and the other half due to restart of medication. These patients received MTX or a combination (54.5%), SSZ or a combination (27.3%), prednisone

Table 2. Numbers and percentages of breastfeeding women 4–6 weeks, 12 weeks, and 26 weeks postpartum in the PARA study and in the general population<sup>17</sup>.

| Variables | RA, PARA Study, n = 249 |           |         | General Population, n = 3009 |           |          |
|-----------|-------------------------|-----------|---------|------------------------------|-----------|----------|
|           | Total                   | Exclusive | Partial | Total                        | Exclusive | Partial  |
| 4–6 weeks | 108 (43) <sup>#</sup>   | 91 (36)   | 17 (7)  | 1896 (63) <sup>#</sup>       | 1625 (54) | 271 (9)  |
| 12 weeks  | 65 (26) <sup>#</sup>    | 47 (19)   | 18 (7)  | 1384 (46) <sup>#</sup>       | 1053 (35) | 331 (11) |
| 26 weeks  | 23 (9) <sup>#</sup>     | 11 (4)    | 12 (5)  | 1233 (41) <sup>#</sup>       | 752 (25)  | 481 (16) |

Values are n (%). <sup>#</sup> P < 0.001 between RA and general population. RA: rheumatoid arthritis; PARA: Pregnancy-induced Amelioration of RA.

Table 3. Reasons for discontinuation of breastfeeding reported by the patients.

| Reasons   | Discontinuation < 6 Weeks<br>Postpartum, n = 141 | Discontinuation 6–12 Weeks<br>Postpartum, n = 43 | Discontinuation 12–26 Weeks<br>Postpartum, n = 39 | Total,<br>n = 223 |
|---|--|--|---|-------------------|
| Restart of medication                             |  |  |   |                   |
| Total   | 86 (61.0)  | 28 (65.1)  | 15 (38.5)   | 129 (57.8)        |
| Not compatible                                    | 51   | 17   | 8   | 76                |
| Compatible  | 35   | 11   | 7   | 53                |
| Maternal reasons                                  | 44 (31.2)  | 14 (32.6)  | 19 (48.7)   | 77 (34.5)         |
| No desire to                                      | 15   | —  | 1   | 16                |
| Not enough milk                                   | 13   | 8  | 12  | 33                |
| Work-related                                      | —  | 4  | 3   | 7                 |
| Too much effort                                   | 7  | —  | 2   | 9                 |
| Mastitis  | 4  | 1  | —   | 5                 |
| Breast surgery                                    | 3  | —  | —   | 3                 |
| Unknown   | —  | 1  | 1   | 2                 |
| Child-related reasons                             | 11 (7.8)   | 1 (2.3)  | 3 (7.7)   | 15 (6.7)          |
| Struggle to latch                                 | 6  | —  | 1   | 7                 |
| Failure to thrive                                 | 4  | 1  | 1   | 6                 |
| Illness   | 1  | —  | 1   | 2                 |
| Combination of maternal and child-related reasons | —  | —  | 1 (2.6)   | 1 (0.4)           |
| Unknown   | —  | —  | 1   | 1                 |
| Unknown   | —  | —  | 1 (2.6)   | 1 (0.4)           |

Values are n (%) unless indicated otherwise.

or a combination (63.6%), HCQ or a combination (18.2%), and nonselective NSAID or a combination (27.3%).

**Disease activity and medication use.** The DAS28-CRP3 changed from 3.1 to 3.4 to 3.0 at 6, 12, and 26 weeks, respectively, after delivery in breastfeeding, and from 3.5 to 3.7 to 3.5 in non-breastfeeding patients (p value at all timepoints between the 2 groups < 0.05).

Medication use postpartum is shown in Table 4. Overall, patients who were not breastfeeding received more medication compared with patients who were breastfeeding. MTX and LEF were exclusively prescribed to non-breastfeeding patients.

**Early discontinuation.** For clinical purposes, the HAQ in the third trimester was dichotomized at the median for easier interpretation (< 0.75 and ≥ 0.75). In univariable analyses,

the HAQ, presence of autoantibodies, smoking periconceptionally or during pregnancy, MTX use in the past, SES, prednisone use in the third trimester, the presence of erosions, and the DAS28-CRP3 in third trimester were associated with discontinuation < 12 weeks (p < 0.20; Table 5).

In the multivariable model, only the HAQ in the third trimester, presence of autoantibodies, and smoking were statistically significant (OR 3.7, 3.2, and 5.9, respectively, and p < 0.001, 0.003, and 0.032, respectively; Table 5). Patients with higher HAQ, patients who were autoantibody-positive, and patients who smoked periconceptionally or during pregnancy were more likely to discontinue breastfeeding within 12 weeks postpartum.

Patients with a HAQ ≥ 0.75 were more likely to restart MTX, LEF, and biologics at 6 or 12 weeks postpartum

Table 4. Disease activity and medication use postpartum.

| Variables                | DAS28-CRP3 | Prednisone | SSZ       | HCQ       | Nonselective NSAID | MTX*      | LEF*    | TNFi*     | Selective COX-2 Inhibitors* | AZA*     |
|--------------------------|------------|------------|-----------|-----------|--------------------|-----------|---------|-----------|-----------------------------|----------|
| <b>Breastfeeding</b>     |            |            |           |           |                    |           |         |           |                             |          |
| 6 weeks, n = 108         | 3.1        | 21 (19.4)  | 23 (21.3) | 0 (0)     | 4 (3.7)            | 0 (0)     | 0 (0)   | 1 (0.9)   | 0 (0)                       | 3 (2.8)  |
| 12 weeks, n = 65         | 3.4        | 15 (23.1)  | 17 (26.2) | 0 (0)     | 9 (13.8)           | 0 (0)     | 0 (0)   | 1 (1.5)   | 1 (1.5)                     | 3 (4.6)  |
| 26 weeks, n = 23         | 3.0        | 3 (13.0)   | 7 (30.4)  | 0 (0)     | 4 (17.4)           | 0 (0)     | 0 (0)   | 0 (0)     | 0 (0)                       | 3 (13.0) |
| <b>Non-breastfeeding</b> |            |            |           |           |                    |           |         |           |                             |          |
| 6 weeks, n = 141         | 3.5        | 65 (46.1)  | 42 (29.8) | 10 (7.1)  | 37 (26.2)          | 46 (32.6) | 0 (0)   | 12 (8.5)  | 8 (5.7)                     | 3 (2.1)  |
| 12 weeks, n = 184        | 3.7        | 75 (40.8)  | 57 (31.0) | 19 (10.3) | 60 (32.6)          | 76 (41.3) | 3 (1.6) | 23 (12.5) | 15 (8.2)                    | 3 (1.6)  |
| 26 weeks, n = 220        | 3.5        | 75 (34.1)  | 63 (28.6) | 18 (8.2)  | 64 (29.1)          | 92 (41.8) | 4 (1.8) | 29 (13.2) | 16 (7.3)                    | 2 (0.9)  |

Values are n (%) unless indicated otherwise. \*Considered not compatible with lactation at the time this study was conducted. DAS28-CRP3: 28-joint count Disease Activity Score using C-reactive protein levels; SSZ: sulfasalazine; HCQ: hydroxychloroquine; NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate; LEF: leflunomide; TNFi: tumor necrosis factor inhibitors; COX-2: cyclooxygenase-2; AZA: azathioprine.

Table 5. Third trimester factors associated with discontinuation of breastfeeding < 12 weeks<sup>#</sup>.

| Variables                      | Univariable        |                      | Multivariable <sup>§</sup> , n = 226 |          |
|--------------------------------|--------------------|----------------------|--------------------------------------|----------|
|                                | OR                 | p                    | OR                                   | p        |
| HAQ, 3rd trimester $\geq 0.75$ | 3.121 <sup>+</sup> | < 0.001 <sup>+</sup> | 3.669*                               | < 0.001* |
| Autoantibody status–positive   | 2.649 <sup>+</sup> | 0.002 <sup>+</sup>   | 3.210*                               | 0.003*   |
| Smoking <sup>%</sup>           | 3.841 <sup>+</sup> | 0.075 <sup>+</sup>   | 5.902*                               | 0.032*   |
| MTX use in past                | 1.857 <sup>+</sup> | 0.034 <sup>+</sup>   | 1.659                                | 0.143    |
| SES based on educational level | 0.696 <sup>+</sup> | 0.156 <sup>+</sup>   | 0.661                                | 0.150    |
| Prednisone use, 3rd trimester  | 3.378 <sup>+</sup> | 0.001 <sup>+</sup>   | 1.924                                | 0.114    |
| Presence of erosions           | 1.693 <sup>+</sup> | 0.071 <sup>+</sup>   | –                                    | –        |
| DAS28-CRP3 3rd trimester       | 1.305 <sup>+</sup> | 0.052 <sup>+</sup>   | –                                    | –        |
| SSZ use, 3rd trimester         | 0.991              | 0.980                |                                      |          |
| VAS global health              | 0.999              | 0.474                |                                      |          |
| Maternal age                   | 0.989              | 0.774                |                                      |          |
| Parity $\geq 1$                | 1.106              | 0.737                |                                      |          |

<sup>#</sup> Based on logistic regression. <sup>§</sup> Multivariable model after forward selection (limit for inclusion:  $p < 0.20$ ) and backward selection (limit for exclusion:  $p \geq 0.20$ ). <sup>%</sup> Smoking periconceptionally or during pregnancy. <sup>+</sup> Variables taken forward if  $p < 0.20$ . \* Statistically significant in the multivariable model. HAQ: Health Assessment Questionnaire; MTX: methotrexate; SES: socioeconomic status; DAS28-CRP3: 28-joint Disease Activity Score using C-reactive protein levels; VAS: visual analog scale; SSZ: sulfasalazine.

compared with patients with a HAQ < 0.75 ( $p = 0.001$ ). In addition, in patients with a HAQ  $\geq 0.75$ , the disease activity postpartum was higher compared with patients with a HAQ < 0.75 (DAS28-CRP3 3.8 vs 3.3;  $p = 0.001$ ).

Also, patients who were autoantibody-positive were more likely to restart MTX, LEF, and biologics at 6 or 12 weeks postpartum compared with patients who were autoantibody-negative ( $p = 0.019$ ). The autoantibody-positive patients had higher disease activity postpartum compared with autoantibody-negative patients (DAS28-CRP3 3.7 vs 3.2;  $p < 0.001$ ).

In the subgroup including only the first participation of the patients ( $n = 216$ ), similar results for the regression models were obtained (data not shown).

## DISCUSSION

In this large nationwide prospective study, we have shown that women with RA are less likely to breastfeed their offspring compared with women from the general (reference) population. More than half (57%) of the patients discontinued breastfeeding before 6 weeks. At 12 weeks only 26% of the patients were still breastfeeding (exclusively and partially combined) compared with 46% in the reference population. At 6 months postpartum the difference was extremely large (9% vs 41%, respectively).

The majority of the patients reported that they discontinued breastfeeding owing to the restart of medication. However, more than 40% of the patients ceased breastfeeding before starting medication that was considered compatible with lactation, according to guidelines from the time this study was conducted (prednisone, SSZ, HCQ, and/or non-selective NSAID). Cessation while using compatible medication was therefore not related to a specific antirheumatic drug. The only exception was HCQ, which was prescribed to

4 women during pregnancy, and none during breastfeeding. However, because of the small numbers, a coincidence cannot be ruled out. This cessation of breastfeeding while using compatible medication could therefore perhaps be due to a general fear of taking medication when breastfeeding, a lack of knowledge, or generic preferences of women to not take any medication while breastfeeding. Unfortunately, in our study it was not assessed whether patients themselves did not feel comfortable breastfeeding when taking medication or whether this was discouraged by their physician. Retrospectively collecting data on this subject was not possible, because our study was a nationwide prospective study, and patients were recruited by rheumatologists from different hospitals all over the country. Also, we did not have informed consent from the patients to contact their rheumatologist to gather information on this subject.

Other reasons for discontinuation included maternal and child-related reasons. Besides restart of medication, most reasons for cessation in this study were comparable with the general population<sup>23</sup>. Work-related discontinuation of breastfeeding was reported in 7.7% of the patients in our study compared with 13.9% in the general population ( $p = 0.05$ )<sup>23</sup>. The most likely explanation for this difference is the lower proportion of paid employment among patients with RA<sup>24,25</sup>.

Higher HAQ in third trimester, presence of autoantibodies, and maternal smoking were significantly associated with discontinuation of breastfeeding at < 12 weeks. It is conceivable that the HAQ and autoantibody status were related to the severity of RA. In our study population, patients with higher HAQ and patients who were autoantibody-positive had higher disease activity postpartum, and were more likely to restart MTX, LEF, and biologics at 6 or 12 weeks postpartum. It therefore makes sense to conclude that both a high HAQ as well as autoantibody positivity

identify patients who have a higher burden of disease and are therefore more likely to require additional medication postpartum, prohibiting them from breastfeeding.

In addition, because the HAQ is a measure of functional status<sup>26</sup>, it is likely that patients with higher HAQ discontinued breastfeeding as a result of functional impairment, either owing to the physical difficulties associated with breastfeeding, or to their need for strong antirheumatic medications.

Further, maternal smoking was associated with early cessation of breastfeeding. Smoking was not related to medication use or disease activity postpartum. It is known that women with lower SES are more likely to smoke during and after pregnancy, and are less likely to breastfeed their offspring<sup>27,28,29,30,31</sup>. Although breastmilk loses many of its health-promoting properties when the mother smokes, smoking mothers are advised not to discontinue breastfeeding<sup>32</sup>. Unfortunately, in our study the number of smoking mothers was too small to study associations with SES. Also, SES was included in the multivariable model, and maternal smoking was independently associated with discontinuation of breastfeeding within 12 weeks, regardless of SES. In our reference population, there were no data on smoking or SES; therefore, we could not make a comparison with our reference group.

In addition, RA patients with offspring with low birth weight also require additional awareness. It has been shown that preterm infants with (very) low birth weight benefit the most from breastmilk<sup>5</sup>. In our study cohort, 85% of the mothers with an offspring with a birth weight < 2500 g discontinued breastfeeding < 6 weeks postpartum, while the mean DAS28-CRP3 postpartum was comparable in both birth weight groups (data not shown). About half of the patients with an offspring < 2500 g reported discontinuation because of the restart of medication. According to the guidelines at the time we performed this study, SSZ was considered incompatible with lactation in ill, stressed, or premature infants<sup>13,14</sup>. However, in that regard, patients receiving prednisone, HCQ, and nonselective NSAID could have continued breastfeeding. In our reference population, there were no data on low birth weight infants; therefore, we could not compare our data with the reference group. Few publications on breastfeeding in low birth weight infants are available. In the Netherlands (2000–2003), 50% of the infants with a birth weight  $\leq$  3000 g were breastfed at 4 weeks postpartum<sup>23</sup> compared with 38% in our study population ( $p = 0.06$ ). Outside the Netherlands, the results were not consistent. Some studies report similar numbers of lactation in low birth weight infants<sup>33,34</sup> compared with healthy infants, while others<sup>35,36</sup> report lower numbers.

Another interesting finding from our study is that the DAS28-CRP3 postpartum was significantly lower in breastfeeding patients compared with non-breastfeeding patients, even though the breastfeeding patients took fewer medica-

tions (when divided into breastfeeding and non-breastfeeding patients at every timepoint). This seems in contrast to the results of a previous study<sup>1</sup> that reported that first-time breastfeeding (but not breastfeeding after subsequent pregnancies) was associated with a significantly greater increase in RA disease activity postpartum compared with non-breastfeeders. In that study, the change in disease activity from the third trimester to 6 months postpartum was compared and breastfeeding was defined as lactating for  $\geq$  4 weeks. When a similar analysis was performed in our study, no such association between first-time breastfeeding and an increase in RA disease activity could be observed (data not shown). The difference is perhaps due to the different time period of that study, when rheumatologists were more reluctant to treat pregnant and lactating women. Another factor is that disease activity was assessed with different methods. Although women with less severe disease are more likely to start and continue breastfeeding, the results of our study do not support the hypothesis that breastfeeding itself causes an increase in RA disease activity<sup>1</sup> (e.g., by inducing high levels of prolactin).

The results of our study will help to develop intervention strategies to support RA patients who wish to breastfeed. First, because a large proportion of patients with RA do not start or continue breastfeeding even though they are taking medication that is compatible, education on medication use during lactation may be valuable for patients and their doctors. Not only rheumatologists but also specialized nurses, midwives, and lactation consultants should be trained to increase their knowledge on this subject. Access to up-to-date medication resources for patients and their clinicians (e.g., evidence-based online databases) is required.

Other patient groups that may benefit from targeted breastfeeding support include patients with offspring with low birth weight and patients who smoke. Further, because functional impairment might influence the start and duration of breastfeeding, ergonomic recommendations should be provided especially to patients with high HAQ.

The results of our study clearly show that a substantial number of patients do not breastfeed because they are in need of medication that is considered incompatible with breastfeeding. In this regard, it is important to realize that guidelines on antirheumatic drug prescription during lactation are often not based on proven side effects or toxicity for the offspring but on lack of safety data of those drugs, especially on transfer of medication into breastmilk<sup>13</sup>. This holds true for many medications, including MTX, one of the “cornerstones” of RA treatment. The authors urge that more research into this particular field be undertaken. That such research, although difficult to perform, is feasible, is shown by a recent study on the lack of transfer of certolizumab into breastmilk<sup>37</sup>.

This study has some limitations. First, it was conducted about 10–16 years ago, and antirheumatic medication

prescriptions have changed. However, we identified that there is a large group of patients who discontinue breastfeeding unnecessarily while using compatible antirheumatic drugs. This might reflect a lack of knowledge on this subject. It is questionable whether the knowledge of doctors and nurses on this specific subject and subsequent education of patients in the clinical practice have improved. Nevertheless, it would be interesting to perform a similar study on breastfeeding by patients with RA in this era of biologic therapies.

Second, a total of 33 women participated more than once in this study. To exclude possible selection bias in the obtained results, we performed a subgroup analysis, including only the first participation of the patients, and found comparable results.

Our study demonstrates that RA is associated with lower proportions of women breastfeeding their offspring and earlier cessation compared with the general population. A considerable number of patients discontinue breastfeeding (unnecessarily) so that they can start medication, even though many of the medications are considered safe to use during lactation. Given the known benefits of breastfeeding on the offspring, more effort in education in the clinical practice and more research into the transfer of medication into breastmilk might enable more patients with RA to breastfeed.

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