Graduate thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences

Helene Eggen

Rheumatoid Arthritis and Breastfeeding

Graduate thesis in Medicine
Supervisor: Marianne Wallenius
Co-supervisor: Agnete Malm Gulati
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Abstract

Objective:

To examine the proportion of women with rheumatoid arthritis (RA) who were breastfeeding, compared to non-breastfeeding, at respectively six weeks, six months and 12 months postpartum, and study the impact of demographic variables, disease characteristics and medications.

Methods:

Data from RevNatus, a Norwegian nationwide prospective observational register, including women with RA who had given birth and had data from at least one of the follow-up controls postpartum, was used. The study included 240 pregnancies in 218 patients.

Results:

The proportion of women breastfeeding was 83% at six weeks, 69% at six months and 41% at 12 months postpartum. Six months after delivery we found that the mean C-reactive protein (CRP) value for the non-breastfeeding group was significantly higher compared to the breastfeeding group (mean CRP-value: 6.4 mg/L vs. 3.2 mg/L, $p = 0.006$). In addition, in the non-breastfeeding group 24 patients (46%) used conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) compared to 33 patients (27%) in the breastfeeding group ($p = 0.02$). At 12 months there were significantly more anti-citrullinated protein antibody (ACPA) positive women breastfeeding than not breastfeeding (37 (73%) vs. 33 (49%), $p = 0.01$).

Conclusion:

This prospective study on women with RA showed that a high proportion were breastfeeding during the first six months after delivery. At six months after delivery the non-breastfeeding women had a significant higher mean CRP-value, and a higher proportion of the non-breastfeeding women used csDMARDs compared to the breastfeeding women.

Sammendrag

Mål:

Undersøke andelen kvinner med revmatoid artritt (RA) som ammer sammenlignet med ikke-ammende ved henholdsvis 6 uker, 6 måneder og 12 måneder etter fødsel, samt å undersøke om demografiske variabler, sykdomskarakteristika eller medikamentell behandling påvirket ammefrekvensen.

Metode:

Kvinner med RA inkludert i det landsdekkende kvalitetsregisteret RevNatus og med data fra minst en av oppfølgingskontrollene etter fødsel, ble inkludert i analysene. Disse utgjorde i alt 218 kvinner med 240 fullførte svangerskap.

Resultater:

Andelen kvinner som ammet var 83% ved 6 uker, 69% ved 6 måneder og 41% ved 12 måneder etter fødsel. Ved 6 måneder etter fødsel hadde den ikke-ammende gruppen signifikant høyere gjennomsnittlig C-reaktivt protein (CRP)-verdi sammenliknet med den ammende gruppen (gjennomsnittlig CRP-verdi: 6.4 mg/L vs. 3.2 mg/L, $p = 0.006$). I tillegg var det 24 (46%) ikke-ammende pasienter som brukte sykdomsmodifiserende medikamenter sammenliknet med 33 (27%) pasienter blant de ammende. Ved 12 måneder var 37 (73%) av kvinnene som ammet positive for anti-citrullinerte antistoffer (anti-CCP), sammenliknet med 33 (49%) av kvinnene som ikke ammet ($p = 0.01$).

Konklusjon:

Studien viste at en høy andel av kvinner med RA ammer de første 6 månedene etter fødsel. Ved 6 måneder etter fødsel hadde ikke-ammende kvinner høyere gjennomsnittlig CRP-verdi og en høyere andel brukte sykdomsmodifiserende medikamenter sammenliknet med ammende kvinner.

Preface

My medical student thesis is based on data collected from the RevNatus register which is a consent-based nationwide Norwegian prospective observational register, operated by the Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases (NKSR) since 2006. The thesis is covering a topic that has not been studied a lot before, and can therefore be a contribution to more knowledge within the field of breastfeeding and RA.

My supervisor, Marianne Wallenius, is a Professor in Rheumatology, Senior Consultant at the Department of Rheumatology, St. Olav´s Hospital. In addition, I had a co-supervisor for this project, Agnete Malm Gulati, Rheumatologist and PhD, Department of Rheumatology at St. Olav´s Hospital.

I would like to thank my supervisor, Marianne Wallenius, for giving me the opportunity to do this project. I really appreciate everything Marianne and Agnete have done for me, being available and helpful whenever needed, and for improving my work with constructive comments and ideas throughout the whole process. Thank you for sharing your wisdom and experience with me.

Lastly, I would like to thank all the patients participating in this study, the NKSR for running and collecting patients to the register on a daily basis, Hege Koksvik for the help of preparing the raw data file, and for answering all my questions about the file, and my fellow student for helping me answer questions regarding statistics, and for the daily motivation we have been giving each other during this special period of time not being able to meet up as much as we have wanted to.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory joint disease characterized by synovitis of the joints, however other organs, such as the lungs and heart, can also be affected (1). The disease can cause severe joint damage, disability and decreased quality of life (2). Smoking and family history of rheumatic disease are well known risk factors of RA, and women of childbearing age are often affected by the disease (3).

Criteria for RA have been developed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) and include the presence of at least one swollen joint (4). Presence of rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA) are biochemical markers of the disease, and systemic inflammation with elevated levels of C-reactive protein (CRP) or erythrocyte sedimentation rate (ERS) is also a hallmark of the disease (3). Presence of ACPA and/or RF has been associated with increased risk of disease activity in pregnancy (5).

Pregnancy outcomes in patients with RA is shown to be less favourable compared with the general population (6). Low disease activity before conception is advised for all women with RA, as this has shown to improve pregnancy outcome (7). Disease activity in RA may improve during pregnancy, however about half of the patients experience relapse postpartum (1, 8). Women with RA should be followed by a rheumatologist before, during and after pregnancy (7). Close monitoring also by an obstetrician is important; because of increased risk of pregnancy complications such as intrauterine growth retardation, low birth weight, or premature birth (1). Up to 50% of women with RA will need treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as sulphasalazine or biological DMARDs (bDMARDs) such as tumor necrosis factor inhibitors (TNF-inhibitors) during pregnancy (1). Since disease flares often occur postpartum, it is also important to follow the patients after delivery.

It is well established that breastfeeding carries numerous benefits for both mother and child (9). The World Health Organization recommends that infants are exclusively breastfed until the age of six months, and that breastfeeding continues until the age of two years (10). Data show that fewer women with RA breastfeed compared to healthy women (11). Most of the existing publications addressing RA and breastfeeding concentrate on the safety of medications commonly used in the treatment of RA, for example transfer of medications into breast milk, whether it influences lactation or causes harm to the infant (12, 13).

The objective of this study was to examine the proportion of women with RA who breastfeed at respectively six weeks, six and 12 months postpartum, and compare the groups

in terms of age, parity, medical treatment, health related quality of life and disease activity. For the patients who terminated use of DMARDs during pregnancy we wanted to explore when DMARDs were restarted after delivery. Further we investigated the use of contraceptives postpartum.

Patients and Methods

The RevNatus-register

Data used in this study was collected from the RevNatus register, a consent-based nationwide Norwegian prospective observational register, operated by the Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases (NKSR) since 2006. From January 1st 2016, the register became a nationwide quality register based on electronic registration, and information about breastfeeding was included. The register collects data on women from 16 years of age diagnosed with inflammatory joint diseases, connective tissue diseases or vasculitis. Data are registered at inclusion, in every trimester of pregnancy, and six weeks, six months and 12 months postpartum, yielding seven registrations in total (14, 15).

Patient Population

This study included patients in RevNatus diagnosed with RA from January 1st 2016, to September 1st 2021. All women fulfilled the EULAR/ACR criteria (4). Only women with data from at least one of the follow-up controls postpartum were included. Women who had not conceived or given birth, and pregnancies not resulting in live births, were excluded.

Data Collection and Outcome Variables

Demographic data included age, work status, education, parity, disease duration, body mass index (BMI), tobacco use (smoking and/or snuff use), and exercise/activity level. Disease specific information on the visual analogue scale (VAS) pain and VAS fatigue, the Modified Stanford Health Assessment Questionnaire (MHAQ), the Disease Activity Score-28-CRP (DAS28-CRP-score), CRP-level, serology with RF and/or ACPA status, and also medications used before pregnancy, were collected.

BMI was categorized into the groups underweight (<18.5 kg/m^2), normal weight (18.5-25.0 kg/m^2) and overweight (>25.0 kg/m^2).

Work status was reported as two categories (working or not working), where part time workers were categorized as working. Students, work absence due to parental leave or chronic disease were categorized as not working.

The category “higher education” included women who had completed a college and/or university degree (> 13 years of school).

Level of exercise was reported as three or more times per week, one to two times per week, one to three times per month or less, however the data was transformed into a binary categorical variable where those answering to some degree of exercise were categorized as “regular exercise” and the remaining as “not regular exercise”.

DAS28-CRP-3 is a disease activity score specific for RA. This is a combined score that includes 28 joint counts for swollen and tender joints combined with the level of CRP (16). DAS28-CRP-3 is considered the best index to evaluate disease activity in pregnant women with RA (15). EULAR has defined four categories of disease activity level based on the DAS28-CRP-3 score: remission if DAS28≤ 2.6, low disease activity if 2.6 <DAS28≤ 3.2, moderate disease activity if 3.2 <DAS28≤ 5.1 and high disease activity if DAS28> 5.1. A score change of ≥ 1.2 is considered clinically significant (16).

Self-reported data, such as the MHAQ for physical functioning, and VAS for pain and fatigue, was collected at each visit. MHAQ consists of eight questions, composed from each of the original HAQ categories, and describes the ability to perform a certain task involved in daily living on a scale from 0 to 3 (0 = no impairments, 3 = not able to perform) (17).

Lactation status (breastfeeding or not breastfeeding) and demographical data are registered at each visit at six weeks, six months and 12 months after birth. The use of DMARDs at each visit was also registered.

Data relevant to pregnancy outcome is collected at the visit six weeks after delivery, including date of birth, date of term, gestational age, birth weight and sex of the infant, delivery method (vaginal, caesarean section – acute or elective), and preeclampsia, eclampsia or Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome during the pregnancy. Analysis of delivery method was stratified in two groups, vaginal delivery and caesarean section (acute and elective).

Data and Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27. Statistical significance level was defined as two-sided p-value ≤ 0.05 with no adjustment made for multiple comparisons. Values are expressed as mean ± SD, or median with interquartile ranges (IQR). Independent student t-test was used for continuous normally distributed variables, such as the patients age, to compare the two groups of breastfeeding versus non-breastfeeding women. Crosstabulations and chi-square tests were used to compare frequencies

between the groups. This was used for all of the dichotomous variables. For these tests we used the Fisher's exact test to estimate the p-value. For all of the other continuous data that were not normally distributed, such as the VAS scores, BMI, DAS28-CRP3 score, MHAQ score, and CRP, we used the Mann-Whitney-U test to estimate p-value. For the BMI, DAS28-CRP3 score, MHAQ score and CRP, we used mean ± SD and for the VAS scores we used the median with IQR.

Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics (REK-Midt, 178044). Before inclusion into the RevNatus register, all of the patients received information about the register and signed a written consent form.

Results

Patient Inclusion Data

Between January 2016 and September 2021 266 pregnancies in 229 women with RA was registered in RevNatus. This is due to the fact that some women are registered with several pregnancies. In this period, 26 pregnancies did not result in live birth, either because of abortion or intrauterine death. There were 11 women that did not fulfil the criteria for inclusion in the study. Thus, the present study comprised a total of 240 pregnancies in 218 patients with RA, as shown in Figure 1. Two pregnancies occurred in 22 women and twin pregnancies occurred in six women. As shown in Figure 1, not all women attended all visits, and these were registered as missing data.

Demographics

Demographical data and disease related characteristics are shown in Table 1. Mean maternal age at inclusion was 31.9 years and mean duration of RA was 5.9 years. The mean DAS28-CRP3 score was 2.46 at inclusion, and the mean MHAQ score at inclusion was 0.25. At inclusion 144 patients (60%) were nulliparous while 70 patients (29%) were para 1, and 26 of the patients (11%) were para 2 or more at inclusion. There were 133 patients (59%) in the normal weight category. At inclusion, four of the patients (2%) were smoking and 12 patients (5%) were using snuff tobacco. In total there were 183 patients (77%) working at the time of inclusion, and 182 (78%) of the patients had a high educational level. There were 105 patients (60%) exercising on a regular basis. Status on RF and ACPA were available for 205 and 208 patients respectively, and 111 patients (54%) were RF positive and 126 patients (61%) were ACPA positive.

The reported median for VAS pain was 18.5, for VAS fatigue 24.0 and for VAS total 19.0. A group of 62 patients (27%) had a CRP level above 5 mg/L at inclusion.

Among the 240 pregnancies, 68 patients (28%) used a csDMARD, 87 patients (36%) used a bDMARD, 24 patients (10%) used Plaquenil and only one patient used a targeted synthetical DMARD (tsDMARD).

Six weeks postpartum

Six weeks postpartum 198 women (83%) were breastfeeding, and 36 women (15%) were not breastfeeding. Data on breastfeeding status was missing for six women. We did not detect any significant differences between the groups when analysing the following variables: age, disease duration, BMI, educational level, level of exercising, DAS28-CRP3 score, ACPA status, and CRP score. More in-depth information on these and other variables are found in Table 2. Non-breastfeeding women had a mean disease duration at 6.8 years, compared to 5.7 years in the breastfeeding women, however the difference was not statistically significant ($p = 0.22$).

At six weeks significantly more non-breastfeeding women (9%) reported use of tobacco-snuff than those who were breastfeeding (2%) ($p = 0.04$). We observed a tendency that breastfeeding women used bDMARDs more often than non-breastfeeding women, but the difference did not reach statistically significance.

Six months postpartum

Six months postpartum 120 women (69%) reported breastfeeding their children, while 53 women (31%) did not breastfeed. At this visit the non-breastfeeding group had a mean CRP-value of 6.4 mg/L compared to the breastfeeding group which had a mean CRP-value of 3.2 mg/L ($p = 0.006$). Grouping the values into elevated CRP (CRP >5) or normal CRP (CRP <5) showed that 12% of the patients in the breastfeeding group had elevated CRP compared to 36% in the non-breastfeeding group ($p = 0.001$).

There was a significant difference in the use of csDMARDs at six months between the two groups, 46% of the non-breastfeeding women used csDMARDs, compared to 28% of the breastfeeding women ($p = 0.02$).

Tobacco snuff use at six months postpartum differed slightly between the two groups (10% of the non-breastfeeding women were using snuff at six months compared to 3% of the breastfeeding women, $p = 0.05$).

The analyses looking at preterm birth, birth weight and pre-eclampsia, eclampsia and HELLP-syndrome were not included in Table 3. There were no differences in these analyses compared to the six weeks postpartum numbers and were therefore not included.

Twelve months postpartum

The 12 months visit included data on 138 pregnancies, where 57 of the women (41%) were still breastfeeding and 80 of the women (58%) were not breastfeeding. Breastfeeding status of one patient was missing. Again, the two groups were comparable regarding most of the demographical and disease specific variables, however the mean age of the breastfeeding women at 12 months postpartum was 35 years compared to 33 years of the non-breastfeeding women ($p = 0.04$). Among the women still breastfeeding at 12 months, 37 (73%) were ACPA positive compared to 33 (49%) of the women not breastfeeding, and this was statistically significant ($p = 0.01$).

Contraception

When looking at the collection of contraceptive data, there is a lot of missing data. At six weeks there is missing data from 74 patients, at six months there is missing data from 33 patients and at 12 months there is missing data from 41 patients. There were no significant differences between the breastfeeding and non-breastfeeding groups at any of the follow-up controls. At six weeks postpartum 59 patients (36%) had started to use contraceptives again, 87 patients (62%) at six months and 69 patients (63%) at 12 months.

Discussion

This study showed a rate of breastfeeding in women with RA at six weeks, six and 12 months after delivery of respectively 83%, 69% and 41%. In breastfeeding and non-breastfeeding women with RA, most demographical and disease related variables, such as age and disease duration, disease activity and RF- and ACPA status were comparable. However, at six months postpartum the non- breastfeeding women had a higher mean CRP than the breastfeeding group. Further, a statistically significantly higher proportion of the non-breastfeeding women used csDMARDs compared to the breastfeeding group. These differences may reflect a higher disease activity among the non-breastfeeding women and contribute to the breastfeeding status six months after delivery.

Comparing the mean age in breastfeeding and non-breastfeeding women at 12 months postpartum, we found that breastfeeding women were slightly older. This has also been

shown in other studies (18). We did not find any significant differences in rate of breastfeeding when comparing nulliparous and multiparous women with RA. We observed that ACPA positive women were breastfeeding longer than ACPA negative women, but we do not have any good explanation for this observed difference.

We found that the non-breastfeeding women reported a significantly higher use of tobacco snuff than the breastfeeding women at the six weeks postpartum control. This could be a random finding due to the fact that there was a very small number of women in each group actually using it and should therefore not be overinterpreted.

This study did not show any significant differences regarding use of contraception between the two groups, however because of missing data, this should be interpreted with caution.

Data from a Norwegian nationwide study from 2013 (18) on breastfeeding rates in healthy women were comparable to our data on women with RA. At six weeks 91% of the women in the general population were breastfeeding compared to 83% of the women with RA in our study. Further, 69% of the women with RA were breastfeeding at six months compared to 71% in the healthy population. At 12 months postpartum 35% of the healthy women were still breastfeeding, while in our group 41% were breastfeeding. Thus, the groups were comparable at six and 12 months after delivery, but less women with RA started breastfeeding after delivery compared to data from the general population.

Throughout the study period most patients had low disease activity. Disease activity in pregnant women with RA has improved during the last decade (1, 8). This is due to more aggressive treatment of the inflammatory disease during pregnancy, and particularly because TNF-inhibitors have become more commonly used during pregnancy, since they are shown to be compatible with pregnancy and recommended if needed, especially during the first 20 weeks of pregnancy (19). TNF-inhibitors can be started two weeks after delivery, as long as there are no signs of infection, and they are safe to use when breastfeeding (20). Early start of treatment after delivery reduces the chance of disease flares (21). The increasing safety data on the use of TNF-inhibitors during pregnancy and breastfeeding has reassured both medical professionals and patients.

Compared to other studies, our study showed a higher proportion of women with RA breastfeeding, and also a longer duration of breastfeeding. A study from the Netherlands (11), showed that a smaller proportion of women with RA and women from the general population started breastfeeding compared to both Norwegian women with RA and women from the general population (18). However, it is difficult to compare results between different

countries, because the breastfeeding culture may be different from one country to another. In Norway there has been a strong focus on all the benefits of breastfeeding the last two decades, through national campaigns and public information in the primary health care system. There has been a focus on information and breastfeeding guidance since women who receive guidance has shown to be breastfeeding longer than to those who do not receive this (22).

The most important strengths of our study are the size of the study population and the prospective design. Women with RA have been included at their local rheumatology department in the public health service all over Norway, which means that they all have been diagnosed by a rheumatologist and received equal health service. The women in the study did also have a similar demographic background making the population very homogenous. So far, our study is one of very few reports on breastfeeding in women with RA looking at the proportion who breastfed and for how long. Thus, our study contributes to new knowledge about breastfeeding in women with RA.

A limitation of this study is the lack of a healthy control group for comparison. We have therefore compared the breastfeeding rates to data from the general population in Norway, however the data dates back to 2013. The present study was not designed as a case–control study, therefore comparison with healthy controls can only be made indirectly, and the results should be interpreted with caution. Another weakness of the study is the amount of missing data, due to the fact that a lot of the postpartum control questions are self-reported data, and not data collected by the rheumatologist. Data that could have influenced some of our results might therefore be lacking. In addition, we did not have data on the reason the women gave for not breastfeeding, and this is an important issue to study in the future. Further, there are not many studies to compare our data with. This means that some of our findings could be random and not reproducible in other studies.

Conclusion

In the current study we observed high breastfeeding rates in women with RA during the first six months after delivery. At six months after delivery, we found that the non-breastfeeding women had a significantly higher mean CRP-value than the breastfeeding women. In addition, a higher proportion of the non-breastfeeding women used csDMARDs compared to the breastfeeding women.

Figure and tables

Figure 1

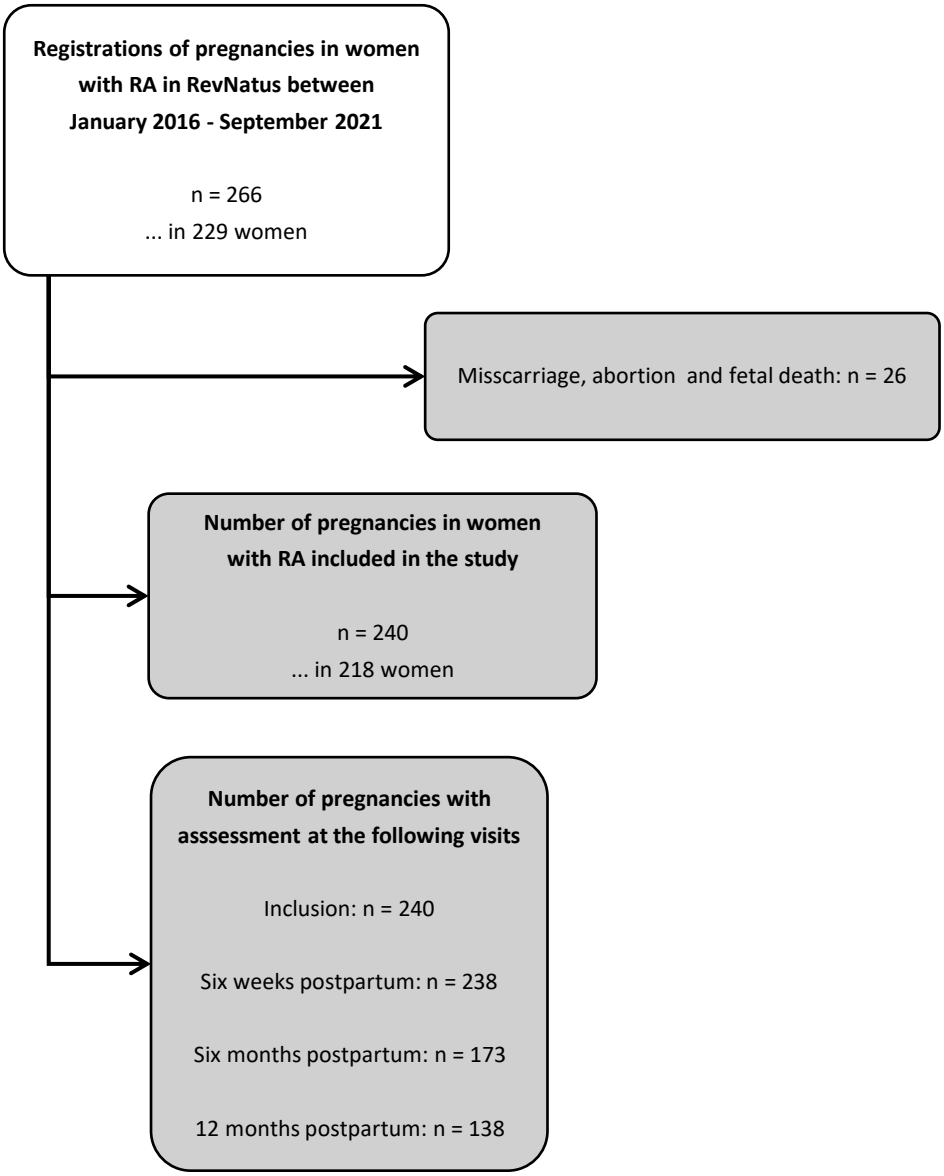


Table 1

Background Characteristics at inclusion among women with RA

Characteristic	n	RA
Number of pregnancies		240
Age, years, mean (SD)	240	31.9 (4.68)
≥ 35 years (n)		67 (27.9%)
Missing		0
Parity	240	
0		144 (60%)
1		70 (29.2%)
2+		26 (10.8%)
Missing		0
Disease duration, years, mean (SD)	216	5.93 (4.79)
BMI, mean (SD)	227	24.7 (5.0)
Underweight (< 18.5)		7 (3.1%)
Normal weight (18,5-25.0)		133 (58.6%)
Overweight (> 25.0)		87 (38.3%)
Missing		13
Smoking	239	4 (1.7%)
Missing		1
Snuff use	228	12 (5.3%)
Missing		12
Educational level	234	
Low		5 (2.1%)
Intermediate		47 (20.1%)
High		182 (77.8%)
Missing		6
Working	237	183 (77.2%)
Missing		3
Exercising on a regular basis	174	105 (60.3%)
Missing		66
DAS28-CRP-score, mean (SD)	217	2.46 (0.89)
≤ 2.6 (remission)		142 (65.4%)

> 2.6 to ≤ 3.2 (low)		30 (13.8%)
> 3.2 to ≤ 5.1 (intermediate)		44 (20.3%)
> 5.1 (high)		1 (0.5%)
Missing		23
VAS pain-score, median (range)	202	18.5 (0-87)
Missing		38
VAS fatigue-score, median (range)	191	24.0 (0-100)
Missing		49
VAS total-score, median (range)	201	19.0 (0-97)
Missing		39
Rheumatic factor positive	205	111 (54.1%)
Missing		35
Anti-CCP/ACPA positive	208	126 (60.6%)
Missing		32
MHAQ-score, mean (SD)	208	0.25 (0.39)
Missing		32
CRP-score, mean (SD)	228	5.23 (6.89)
CRP >5		62 (27.2%)
Missing		12
csDMARDs	240	68 (28.3%)
bDMARDs	240	87 (36.3%)
Plaquenil	240	24 (10%)
tsDMARDs	240	1 (0.4%)

BMI = Body Mass Index, DAS28-CRP = Disease Activity Score-28-CRP, VAS = Visual Analouge Scale, RF = Rheumatic Factor, Anti-CCP= Anti-citrullinated protein antibody, MHAQ = Modified Stanford Health Assessment Questionnarie, CRP = C-reactive protein, csDMARDs = conventional synthetic disease-modifying anti-rheumatic drugs, bDMARDs = biological DMARDs, tsDMARDs = targeted synthetical DMARDs

Table 2

Comparing breastfeeding to non-breastfeeding women with RA at six weeks postpartum

	n (B/N-B)	Breastfeeding (n =198)	Non-breastfeeding (n = 36)	P-value
Age, years, mean (SD)	198/36	32.8 (4.58)	32.7 (4.99)	0.86
≥ 35 years		62 (31.3%)	13 (36.1%)	0.57
Missing	6			
Nulliparous	198/36	120 (60.6%)	21 (58.3%)	0.85

	n (B/N-B)	Breastfeeding (n =198)	Non-breastfeeding (n = 36)	P-value
Missing	6			
Disease duration, years, mean (SD)	178/34	5.7 (4.67)	6.8 (5.47)	0.22
Missing	28			
BMI, mean (SD)	196/33	25.2 (4.65)	27.2 (5.75)	0.11
Overweight (>25.0)		90 (45.9%)	17 (51.5%)	0.58
Missing	11			
Smoking	194/34	1 (0.5%)	0	-
Missing	12			
Snuff use	194/34	3 (1.5%)	3 (8.8%)	0.04
Missing	12			
Educational level	197/36			
Low		4 (2.0%)	1 (2.8%)	0.57
Intermediate		37 (18.8%)	10 (27.8%)	0.26
High		156 (79.2%)	25 (69.4%)	0.20
Missing	7			
Working	198/36	20 (10.1%)	1 (2.8%)	0.21
Missing	6			
Exercising on a regular basis	160/29	58 (36.3%)	12 (41.4%)	0.68
Missing	51			
DAS28-CRP-score, mean (SD)	188/33	2.47 (0.97)	2.52 (0.89)	0.67
Missing	19			
VAS pain-score, median (IQR)	174/30	20 (45)	25 (33)	0.46
Missing	36			
VAS fatigue-score, median (IQR)	171/29	22 (56)	30 (55)	0.34
Missing	40			
VAS total-score, median (IQR)	175/30	20 (45)	34.5 (29)	0.12
Missing	35			
RF positive (inclusion)	171/31	93 (54.4%)	15 (48.4%)	0.56
Missing	38			

	n (B/N-B)	Breastfeeding (n =198)	Non-breastfeeding (n = 36)	P-value
Anti-CCP positive (inclusion)	172/32	103 (59.9%)	19 (59.4%)	1.00
Missing	36			
MHAQ, mean (SD)	185/36	0.31 (0.47)	0.23 (0.30)	0.92
Missing	19			
CRP, mean (SD)	167/32	6.83 (12.7)	8.63 (22.2)	0.86
CRP >5		50 (29.9%)	9 (28.1%)	1.00
Missing	41			
Prematurity	196/36	14 (7.1%)	3 (8.3%)	0.73
Missing	8			
Low birthweight (<2500 g)	194/36	11 (5.7%)	3 (8.3%)	0.47
Missing	10			
C-section	197/36	42 (21.3%)	9 (25.0%)	0.66
Missing	7			
Pre-eclampsia/Eclampsia/HELLP-syndrome	192/36	16 (8.3%)	1 (2.8%)	0.49
Missing	12			
Contraception	142/22	53 (37.3%)	6 (27.2%)	0.48
Missing	76			
csDMARDs	198/36	55 (27.8%)	9 (25.0%)	0.84
Missing	6			
bDMARDs	198/36	52 (26.2%)	4 (11.1%)	0.06
Missing	6			
Plaquenil	198/36	25 (12.6%)	2 (5.6%)	0.39
Missing	6			
tsDMARDs	198/36	0	0	-
Missing	6			

BMI = Body Mass Index, DAS28-CRP = Disease Activity Score-28-CRP, VAS = Visual Analouge Scale, RF = Rheumatic Factor, Anti-CCP= Anti-citrullinated protein antibody, MHAQ = Modified Stanford Health Assessment Questionnarie, CRP = C-reactive protein, csDMARDs = conventional synthetic disease-modifying anti-rheumatic drugs, bDMARDs = biological DMARDs, tsDMARDs = targeted synthetical DMARDs

Table 3

Comparing breastfeeding to non-breastfeeding women with RA at six and 12 months postpartum

	n (B/N-B)	Breastfeeding at 6 months (n = 120)	Non-breastfeeding at 6 months (n = 53)	*p*	n (B/N-B)	Breastfeeding at 12 months (n = 57)	Non-breastfeeding at 12 months (n = 80)	*p*
Age, years, mean (SD)	117/51	33.6 (4.65)	33.2 (5.15)	0.61	55/78	35.0 (4.88)	33.0 (5.69)	0.04
Missing	72				107			
Nulliparous	120/53	71 (59.2%)	32 (60.4%)	1.00	57/80	32 (56.1%)	54 (67.5%)	0.21
Missing	67				103			
BMI, mean (SD)	118/51	24.5 (4.9)	26.4 (6.1)	0.08	57/78	23.8 (3.8)	26.1 (6.0)	0.06
Overweight (>25.0)		43 (36.4%)	21 (41.2%)	0.61		18 (31.6%)	32 (41.0%)	0.28
Missing	71				105			
Smoking	115/50	1 (0.9%)	1 (2.0%)	0.52	56/76	2 (3.6%)	1 (1.3%)	0.57
Missing	75				108			
Snuff use	115/49	3 (2.6%)	5 (10.2%)	0.05	55/75	1 (1.8%)	8 (10.7%)	0.08
Missing	76				110			
Educational level	118/53				56/80			
Low		2 (1.7%)	2 (3.8%)	0.59		0	2 (2.5%)	0.51
Intermediate		19 (16.1%)	11 (20.8%)	0.52		10 (17.9%)	16 (20%)	0.83
High		97 (82.2%)	40 (75.5%)	0.31		46 (82.1%)	59 (73.8%)	0.30
Missing	69				104			
Working	119/53	10 (8.4%)	4 (7.5%)	-	57/80	23 (40.4%)	40 (50%)	0.30
Missing	68				103			
Exercising on a regular basis	102/42	58 (56.9%)	26 (61.9%)	0.71	53/70	33 (62.3%)	44 (62.9%)	1.00
Missing	96				117			
DAS28-CRP-score, mean (SD)	114/52	2.30 (0.76)	2.58 (1.0)	0.08	53/80	2.36 (0.69)	2.41 (0.95)	0.84
Missing	74				107			
VAS pain-score, median (IQR)	109/51	20 (37)	25 (44)	0.64	52/71	12 (35)	21 (41)	0.18
Missing	80				117			

	n (B/N-B)	Breastfeeding at 6 months (n = 120)	Non-breastfeeding at 6 months (n = 53)	*p*	n (B/N-B)	Breastfeeding at 12 months (n = 57)	Non-breastfeeding at 12 months (n = 80)	*p*
VAS fatigue-score, median (IQR)	106/48	28.5 (50)	30.5 (55)	0.96	51/68	24 (46)	31 (60)	0.07
Missing	86				121			
VAS total-score, median (IQR)	107/49	27 (42)	30 (44)	0.78	52/70	17 (49)	28 (46)	0.14
Missing	84				118			
RF positive (inclusion)	104/44	58 (55.8%)	23 (52.3%)	0.72	50/67	31 (62.0%)	32 (47.8%)	0.14
Missing	92				123			
Anti-CCP positive (inclusion)	105/44	69 (65.7%)	24 (54.5%)	0.27	51/68	37 (72.5%)	33 (48.5%)	0.01
Missing	91				121			
MHAQ, mean (SD)	114/50	0.27 (0.38)	0.32 (0.36)	0.26	56/76	0.20 (0.30)	0.26 (0.37)	0.41
Missing	76				108			
CRP, mean (SD)	104/47	3.21 (4.5)	6.43 (9.3)	<0.01	49/73	4.0 (10.0)	3.79 (4.6)	0.08
CRP >5		12 (11.5%)	17 (36.2%)	<0.01		6 (12.2%)	13 (17.8%)	0.46
Missing	89				118			
C-section	118/53	21 (17.8%)	15 (28.3%)	0.16	57/78	10 (17.5%)	23 (29.5%)	0.16
Missing	69				105			
Contraception	93/46	56 (60.2%)	31 (67.4%)	0.46	45/64	28 (62.2%)	41 (64.1%)	0.84
Missing	101				131			
csDMARDs	120/52	33 (27.5%)	24 (46.2%)	0.02	57/80	19 (33.3%)	32 (40.0%)	0.48
bDMARDs	120/52	57 (47.5%)	28 (53.8%)	0.51	57/80	28 (49.1%)	38 (47.5%)	0.86
Plaquenil	120/52	16 (13.3%)	6 (11.5%)	0.81	57/80	8 (14.0%)	10 (12.5%)	0.80
tsDMARDs	120/52	0	1 (1.9%)	0.30	57/80	0	1 (1.25%)	-

BMI = Body Mass Index, DAS28-CRP = Disease Activity Score-28-CRP, VAS = Visual Analouge Scale, RF = Rheumatic Factor, Anti-CCP= Anti-citrullinated protein antibody, MHAQ = Modified Stanford Health Assessment Questionnarie, CRP = C-reactive protein, csDMARDs = conventional synthetic disease-modifying anti-rheumatic drugs, bDMARDs = biological DMARDs, tsDMARDs = targeted synthetical DMARDs

Table 4

Number and proportion of breastfeeding women at six weeks, six and 12 months

	n	Missing	Breastfeeding	Non-breastfeeding
6 weeks	238	4	198 (83.2%)	36 (15.1%)
6 months	173	0	120 (69.4%)	53 (30.6%)
12 months	138	1	57 (41.3%)	80 (58.0%)

Table 5

Use of medications at inclusion, six weeks, six months and 12 months postpartum

	Inclusion (n=240)	6 weeks postpartum (n=234)	6 months postpartum (n=172)	12 months postpartum (n=137)
csDMARDs	68 (28.3%)	64 (27.4%)	57 (33.1%)	51 (37.2%)
bDMARDs	87 (36.3%)	56 (23.9%)	85 (49.4%)	66 (48.2%)
Plaquenil	24 (10%)	27 (11.5%)	22 (12.8%)	18 (13.1%)
tsDMARDs	1 (0.4%)	0 (0%)	1 (0.6%)	1 (0.7%)

csDMARDs = conventional synthetic disease-modifying anti-rheumatic drugs, bDMARDs = biological DMARDs, tsDMARDs = targeted synthetical DMARDs

Table 6

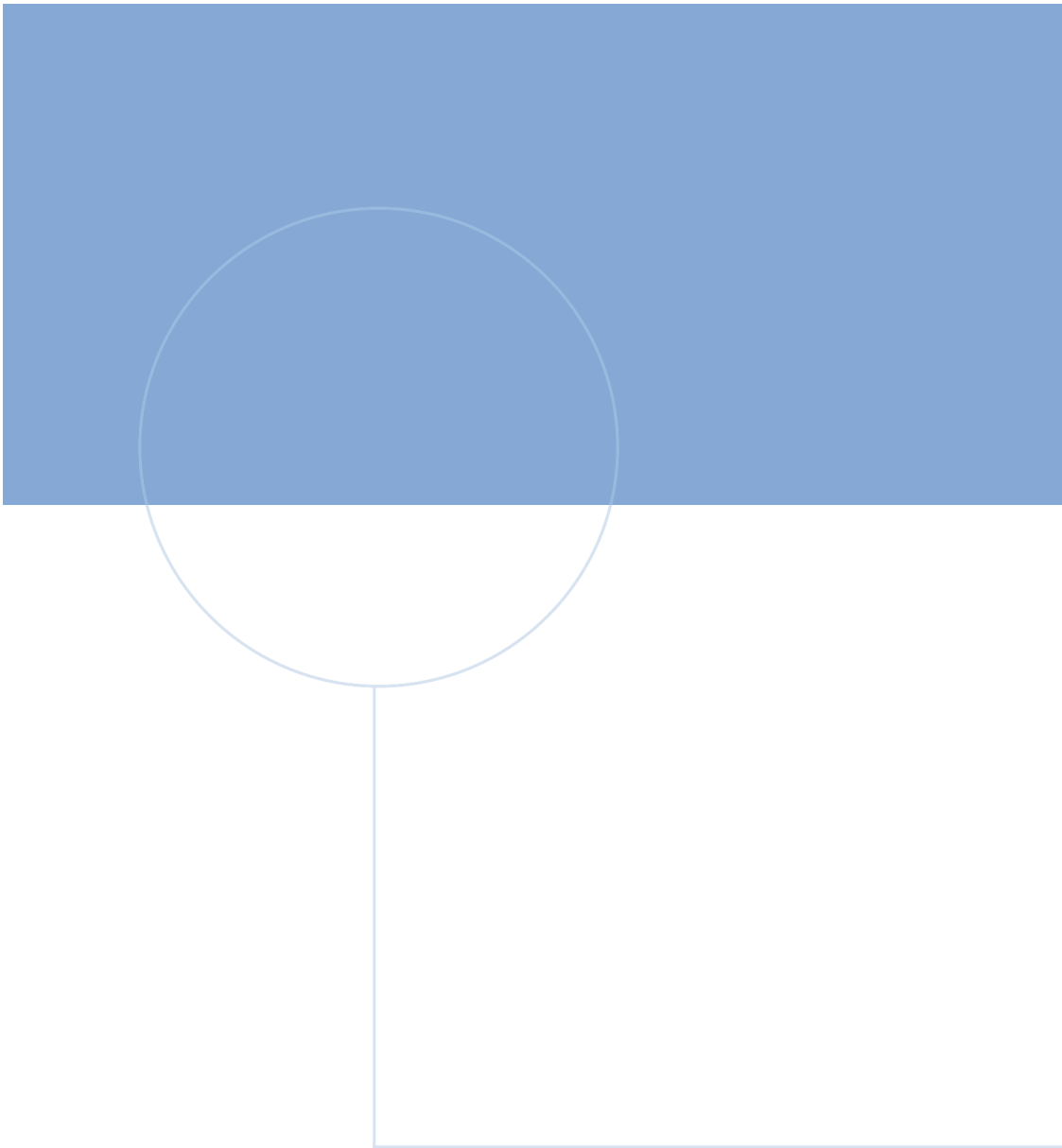
Use of contraception at six weeks, six and 12 months postpartum

	6 weeks postpartum (n = 164)	6 months postpartum (n =140)	12 months postpartum (n = 110)
Using contraceptives	59 (36.0%)	87 (62.1%)	69 (62.7%)
Missing	74	33	28

References

1. Wallenius M, Skomsvoll JF, Salvesen KÅ. Kronisk inflammatorisk artritt og svangerskap. Tidsskrift for Den norske legeforening. 2012.
2. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376:1094-108.
3. Wasserman AM. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 2011;84:1245-52.
4. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford). 2012;51:5-9.
5. Förger F, Vallbracht I, Helmke K., et al. Pregnancy mediated improvement of rheumatoid arthritis. Swiss Med Wkly. 2012;142:13644.
6. Wallenius M, Salvesen K, Daltveit AK, et al. Rheumatoid arthritis and outcomes in first and subsequent births based on data from a national birth registry. Acta Obstet Gynecol Scand. 2014;93:302-7.
7. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Rheumatol. 2020;72:529-56.
8. Jethwa H, Lam S, Smith C, et al. Does Rheumatoid Arthritis Really Improve During Pregnancy? A Systematic Review and Metaanalysis. The Journal of Rheumatology. 2019;46:245-50.
9. Louis-Jacques AF, Stuebe AM. Enabling Breastfeeding to Support Lifelong Health for Mother and Child. Obstet Gynecol Clin North Am. 2020;47:363-81.
10. WHO Guidelines Approved by the Guidelines Review Committee. Infant and Young Child Feeding: Model Chapter for Textbooks for Medical Students and Allied Health Professionals. Geneva: World Health Organization. Copyright © 2009, World Health Organization.; 2009. https://apps.who.int/iris/bitstream/handle/10665/44117/9789241597494_eng.pdf?sequence=1&isAllowed=y
11. Ince-Askan H, Hazes JMW, Dolhain RJEM. Breastfeeding among Women with Rheumatoid Arthritis Compared with the General Population: Results from a Nationwide Prospective Cohort Study. The Journal of Rheumatology. 2019;46:1067-74.
12. Gotestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75:795-810.
13. Sammaritano LR, Bermas BL. Rheumatoid arthritis medications and lactation. Curr Opin Rheumatol. 2014;26:354-60.
14. Meissner Y, Strangfeld A, Costedoat-Chalumeau N, et al. European Network of Pregnancy Registers in Rheumatology (EuNeP)-an overview of procedures and data collection. Arthritis Res Ther. 2019;21:241.
15. Ursin K, Lydersen S, Skomsvoll JF, et al. Psoriatic Arthritis Disease Activity During and After Pregnancy: A Prospective Multicenter Study. Arthritis Care Res (Hoboken). 2019;71:1092-100.
16. Wells G, Becker JC, Teng J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009;68:954-60.
17. Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified

Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). Arthritis Care Res (Hoboken). 2011;63:S4-13.
18. Lande B, Helleve A. Amming og spedbarns kosthold: Landsomfattende undersøkelse 2013. Oslo: Helsedirektoratet, Report No: IS-2239. 2013.
19. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79:685-99.
20. De Felice KM, Kane S. Safety of anti-TNF agents in pregnancy. J Allergy Clin Immunol. 2021;148:661-7.
21. Murray KE, Moore L, O'Brien C, et al. Updated pharmacological management of rheumatoid arthritis for women before, during, and after pregnancy, reflecting recent guidelines. Ir J Med Sci. 2019;188:169-72.
22. Halvorsen M-K, Langeland E, Almenning G, et al. Amming kartlagt ved rutinedata. Tidsskrift for Den norske legeforening. 2015.



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