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Factors Associated With Time to Pregnancy in Women With Axial Spondyloarthritis: A Registry-Based Multicenter Study

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Objective. The present study was undertaken to study time to pregnancy (TTP) and factors associated with TTP in women with axial spondyloarthritis (SpA) compared to women with rheumatoid arthritis (RA).

Methods. We included 274 women with axial SpA and 317 women with RA from the Norwegian nationwide registry RevNatus. For all the women, we had retrospectively collected data on TTP, and a subgroup also had prospectively collected data. We compared TTP in women with axial SpA to women with RA using Kaplan-Meier plots and a log rank test. To identify factors associated with TTP, we used Cox proportional hazards regression.

Results. TTP exceeded 12 months in 21% of women with axial SpA. In the subgroup followed prospectively, 32% had TTP that exceeded 12 months. Longer TTP was associated with older age, nulliparity, and longer disease duration, with hazard ratios of 0.97 (95% confidence interval [95% CI] 0.94–1.00), 0.66 (95% CI 0.50–0.88), and 0.94 (95% CI 0.91–0.98), respectively. Disease activity, medication, and self-reported health-related quality of life were not associated with TTP. We found no statistically significant differences between axial SpA and RA in regard to TTP.

Conclusion. In women with axial SpA, longer TTP was associated with older age, nulliparity, and longer disease duration.

INTRODUCTION

Motherhood is important for many women regardless of whether or not they have a chronic disease. Studies have shown that women with chronic arthritis have lower fertility rates and more often are childless compared to healthy peers (1,2).

Fertility is a person's capacity to achieve pregnancy (3). Time from the start of actively trying to conceive to achieved pregnancy exceeding 12 months is often defined as subfertility (3). The prevalence of subfertility in the general population is estimated to be 9% (4). A study from 2015 demonstrated that 42% of women with rheumatoid arthritis (RA) were subfertile according to the above definition and that longer time to pregnancy (TTP) was associated with older age, nulliparity, disease activity, and use of prednisolone or nonsteroidal antiinflammatory drugs (NSAIDs) (5). Previous studies have found higher occurrence of subfertility in women with RA compared to healthy controls and women with systemic lupus erythematosus (6,7).

Axial spondyloarthritis (SpA) is a chronic inflammatory rheumatic disease affecting the spine, as well as entheses and joints, with common onset in childbearing age (8). Ankylosing spondylitis (AS), now also called radiographic axial SpA because the diagnosis requires established sacroiliitis on radiographs, was traditionally seen as a disease affecting men. After the recognition of nonradiographic axial SpA, which is axial SpA without characteristic findings on radiographs, more women are diagnosed with axial SpA. Including nonradiographic axial SpA, the male:female ratio is 2–3:1 (9). A Norwegian study found that fertility rate and occurrence of childlessness were similar in women with SpA or unspecified arthritis compared to those with RA (2). To our knowledge, there are no studies on TTP in women with axial SpA.

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SIGNIFICANCE & INNOVATIONS

- In this study on time to pregnancy in women with axial spondyloarthritis, more than one-fifth of women were subfertile.
- Longer time to pregnancy was associated with longer disease duration, older age, and nulliparity.
- Findings suggest that young women with stable axial spondyloarthritis should be encouraged not to postpone pregnancy for too long.

Our aim was to study TTP and factors associated with TTP in women with axial SpA. Also, we wanted to compare women who conceived within 12 months to subfertile women with regard to preconception disease activity, health-related quality of life (HRQoL), medication, and factors that are known to affect fertility in the general population. Hypothesizing that fertility in axial SpA is similar to that in RA, we compared women with axial SpA to women with RA.

PATIENTS AND METHODS

RevNatus registry. RevNatus is a Norwegian nationwide registry designed for prospective follow-up of women with inflammatory rheumatic diseases from the time of planning a pregnancy until 1 year postpartum (10). The registry was established in 2006 by the Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases. Enrollment in RevNatus is carried out by rheumatologists and nurses at the collaborating rheumatology units.

Women enrolled in RevNatus ideally have 7 visits at their local rheumatology unit: when planning pregnancy, in each trimester, and at 6 weeks, 6 months, and 12 months postpartum. RevNatus has a prospective design and provides data on disease activity, medication, HRQoL, TTP, and pregnancy outcomes. Although we aim to enroll women in RevNatus when they plan a pregnancy, a minority of women with axial SpA or RA were actually enrolled preconception.

Patient population. This study comprises women with axial SpA or RA enrolled in RevNatus between January 2006 and October 2018. Before 2016, RevNatus did not differentiate between radiographic axial SpA and nonradiographic axial SpA. For the present study, we included women with information on whether they had tried to get pregnant for >12 months or not, and preferably those who had information on the number of months they had tried to conceive. Women were allowed to participate more than once.

Study design and outcome variables. This study has the combination of both a prospective and retrospective design. We studied time trying to conceive in 1) the total study population, where a large proportion was already pregnant at enrollment, and 2) a subgroup of women who enrolled prior to conception. These 2 approaches yield complementary results.

The 2 main outcome variables were subfertility defined as TTP >12 months (yes/no) and TTP (months). The variable TTP >12 months (yes/no) was introduced in RevNatus in 2009, while self-reported TTP (months) was introduced in 2014. We defined TTP as months trying to conceive either resulting in pregnancy or in censoring. For women who enrolled preconception, we collected TTP prospectively either when they became pregnant or at censoring. For women who were already pregnant at the time of enrollment, self-reported data were collected retrospectively. Data were collected from hospital records for women enrolled before 2009. Other outcome variables were achieved pregnancy during the study period, live birth, and receiving fertility treatment.

The variable planned pregnancy (yes/no) was not available in RevNatus before 2016. In the analyses of the total study population, TTP = 0 months means either conceiving within the first menstrual cycle of attempting pregnancy or unplanned pregnancy.

Covariates. A rheumatology health care professional recorded information on disease characteristics, medication history, and prior pregnancies at enrollment in RevNatus. Information on disease activity, current medication, and self-reported HRQoL was recorded at each visit.

Disease activity of axial SpA was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The BASDAI gives scores between 0 and 10 (10 = maximal disease activity) based on 6 patient-reported items (11). The 3-variable Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) was used to measure disease activity in RA. The score is composed of a 28-joint count for swelling and tenderness combined with the level of CRP (12). Where available, we used preconception disease activity as a covariate. For women who were pregnant at enrollment, we used first trimester disease activity.

Self-reported HRQoL was assessed using the RAND Short Form 36 (SF-36) health survey. The SF-36 is composed of 36 questions in 8 health-related dimensions, resulting in 1 score in each dimension with value 0–100 (100 = best possible health) (13). We studied 4 dimensions that theoretically could affect sexual function preconception and the ability to conceive: mental health, vitality, bodily pain, and physical functioning. In analyses, we only used preconception SF-36 scores.

Other covariates were age, parity, smoking, body mass index (BMI), and disease duration. In addition, medication used within 1 year prior to conceiving constituted 4 dichotomous covariates (yes/no): prednisolone, NSAIDs, methotrexate (MTX), and tumor necrosis factor inhibitor (TNFi).

Statistical analysis. We compared women with axial SpA to women with RA with regard to achieving pregnancy, subfertility, TTP, fertility treatment, and giving birth to a live child. Within the axial SpA group, we also compared women who conceived within

12 months to subfertile women with regard to the covariates listed above. We used an independent samples *t*-test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables.

We compared TTP between groups using Kaplan-Meier plots and a log rank test. Furthermore, we used Cox proportional hazards regression models to explore associations between TTP and the covariates listed above in each diagnostic group. In analyses of the associations between TTP and disease duration and parity, we adjusted for age. We use the term "pregnancy ratio" for hazard ratio in Cox regression.

Two-sided *P* values less than 0.05 were considered significant. We compared Cox regression assuming independent times with Cox

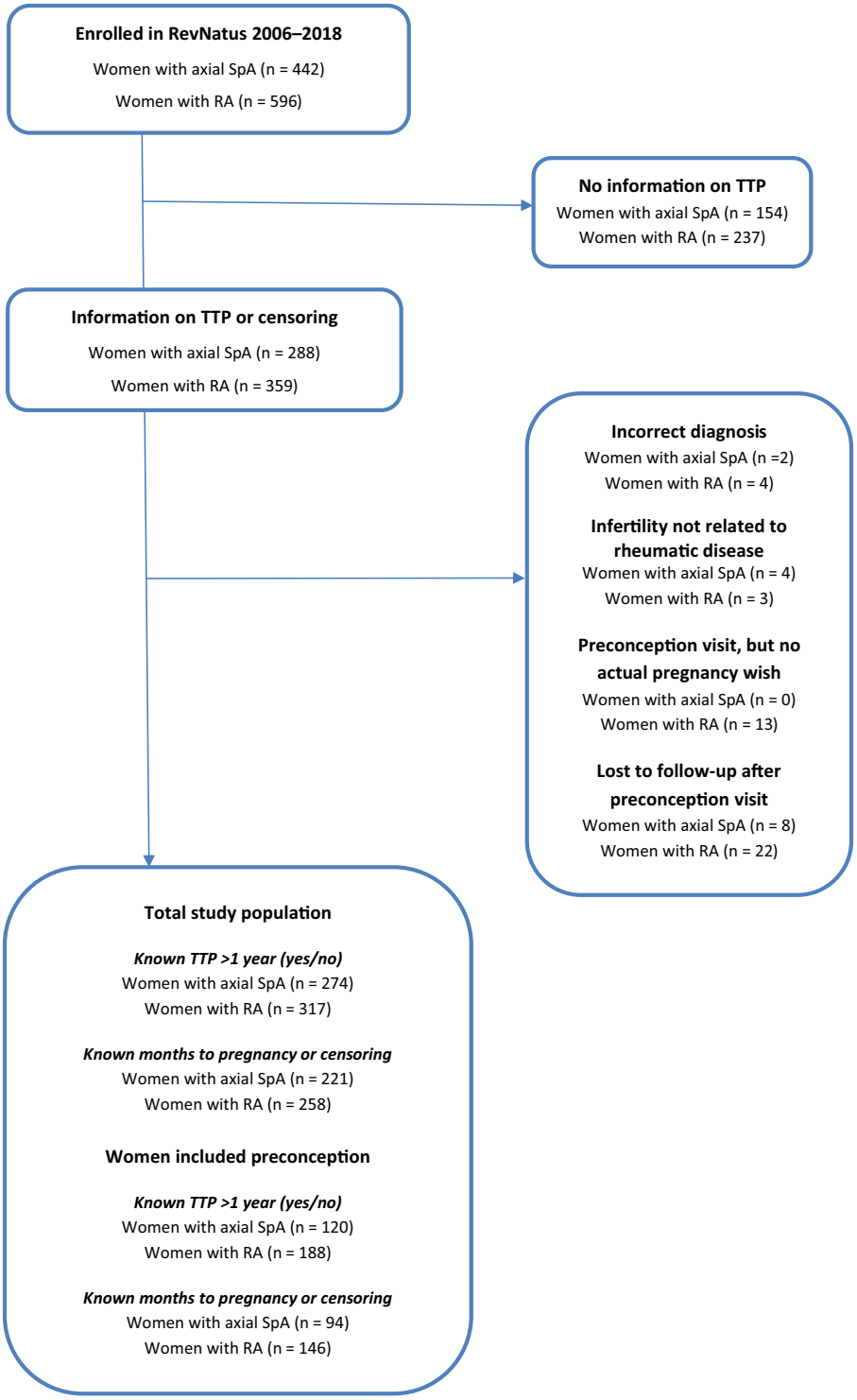

Figure 1. Flow chart showing inclusion data and data available for analyses. RA = rheumatoid arthritis; SpA = spondyloarthritis; TTP = time to pregnancy.

regression with gamma shared frailty, the latter taking into account the possible dependence between TTP in the same woman, using Stata, version 14.0. Other analyses were carried out in SPSS, version 25.0.

Ethics. The regional committee for medical and health research ethics approved this study in 2013 (REK 2013/649). Women enrolled in RevNatus gave written informed consent that data from the registry can be used for research purposes. The study is in compliance with the Declaration of Helsinki.

RESULTS

Patient inclusion data. RevNatus included 442 women with axial SpA and 596 women with RA between January 2006 and November 2018. Of these, we excluded 154 women with axial SpA and 237 women with RA with no information on TTP. Most of the excluded women were enrolled before information on TTP was routinely recorded in RevNatus. In addition, we excluded women with an incorrect diagnosis, no actual wish for pregnancy, or known infertility not related to their rheumatic disease.

As shown in Figure 1, this study comprised 274 women with axial SpA and 317 women with RA, all with data on TTP >12 months (yes/no). Of these, 154 women with axial SpA (56.2%) and 129 women with RA (40.7%) were pregnant at enrollment. Information on TTP was self-reported in 188 (68.6%) of women with axial SpA and 187 (59.0%) of women with RA. The remaining women had information on TTP that was retrieved from hospital records.

Women with information on months trying to conceive were included in the survival analyses. We included 221 women with axial SpA, of whom 94 (42.5%) were enrolled when planning pregnancy, and 258 women with RA, of whom 146 (56.6%) were enrolled when planning pregnancy. Fourteen women with axial SpA and 20 women with RA had not conceived by the end of the study period and hence were censored. Three women with axial SpA and 9 women with RA, who moved or changed their mind about pregnancy, were also censored. After confirming that Cox regression with gamma shared frailty gave the same results as Cox regression assuming independent TTP, we carried out analyses assuming all TTP to be independent.

Demographic and disease characteristics. Women with axial SpA had a median age of 31 years (range 21–46 years) and a median disease duration of 4 years (range 0–26 years). Women with RA had a median age of 32 years (range 19–44 years) and a median disease duration of 5 years (range 0–22 years). More than one-half of the women had previously given birth to a live child. In the axial SpA group, polycystic ovary syndrome was reported in 11 women (4.0%), while endometriosis was reported in 4 women (1.5%).

The majority of the study population fulfilled the Assessment of SpondyloArthritis international Society (ASAS) criteria for axial SpA and the 1987 revised criteria of the American College of Rheumatology for RA, respectively (11,14). Table 1 shows demographics and disease characteristics recorded at enrollment.

Table 1. Characteristics of the study population at baseline*

Basic characteristics	Axial SpA (n = 274)	RA (n = 317)
Age, mean ± SD years	30.7 ± 4.9	31.7 ± 4.7
BMI, mean ± SD kg/m^2	25.1 ± 4.6	25.0 ± 5.0
Smoking		
Yes	264/17 (6.4)	306/12 (3.9)
Parity		
0	272/129 (47.4)	313/155 (49.5)
1	99 (36.4)	117 (37.4)
2+	44 (16.2)	41 (13.1)
Prior pregnancy loss		
Yes	270/69 (25.6)	310/70 (22.6)
Educational level†		
Low	261/11 (4.2)	304/4 (1.3)
Intermediate	69 (26.4)	63 (20.7)
High	181 (69.4)	237 (78.0)
Disease-related characteristics		
Disease duration, years	5.2 (4.6)	6.0 (4.8)
Classification criteria fulfilled‡		
Yes	270/264 (97.8)	310/300 (96.8)
Rheumatoid factor positive		
Yes	NA	275/172 (62.5)
Anti-CCP positive		
Yes	NA	286/186 (65.0)
HLA–B27 positive		
Yes	166/125 (75.3)	NA
Psoriasis	9 (3.3)	NA
IBD§	26 (9.5)	NA
Uveitis	24 (8.9)	NA

* Values are the total no./no. (%) unless indicated otherwise. Anti-CCP = anti–cyclic citrullinated peptide; BMI = body mass index; IBD = inflammatory bowel disease; NA = not available; RA = rheumatoid arthritis; SpA = spondyloarthritis.
† Low: ≤10 years, intermediate: 10–13 years, high: >13 years.
‡ American College of Rheumatology criteria or Assessment of SpondyloArthritis international Society criteria (refs. 11 and 14).
§ Ulcerative colitis: n = 6, morbus Crohn's disease: n = 7, nonspecified IBD: n = 13.

Fertility outcomes in women with axial SpA. In the total axial SpA population, 257 women (93.8%) became pregnant, and 154 (46.2%) were already pregnant at enrollment (Table 2). Median TTP was 2 months, and 58 women (21.2%) had TTP >12 months. Twenty-one women with axial SpA (7.7%) had fertility treatment.

Among the 120 women with axial SpA followed from planning pregnancy, a smaller proportion became pregnant (103 women, 85.8%), and a more substantial proportion was subfertile (38 women, 31.7%). The median TTP was 4 months. Among the 93 women with axial SpA enrolled preconception and followed until after delivery, 75 women (80.6%) had a live birth.

Differences between fertile and subfertile women. Subfertile women with axial SpA were significantly older and had a significantly longer disease duration than women with axial SpA who conceived within 12 months (Table 3). They were also significantly more likely to be nulliparous and have been smokers prior to conception. There were no differences with regard to disease activity or medication.

Table 2. Fertility-related outcomes*

Outcomes	Axial SpA	RA	*P*
Total study population			
Achieved pregnancy	274/257 (93.8)	317/288 (90.9)	0.18†
Months to pregnancy, no.	204	229	
Mean ± SD	5.8 ± 12.1	6.9 ± 15.4	0.41‡
Months to pregnancy or censoring, no.	221	258	
Median (range)	2 (0–126)	3 (0–137)	0.12§
Time to pregnancy >1 year¶	58 (21.2)	75 (23.7)	0.47†
Fertility treatment[1]			
Yes	253/21 (8.3)	290/38 (13.1)	0.07†
Included preconception			
Achieved pregnancy	120/103 (85.8)	188/159 (84.6)	0.76†
Live birth#			
Yes	93/75 (80.6)	147/124 (84.4)	0.45†
Months to pregnancy or censoring, no.	94	146	
Median (range)	4 (0–113)	3 (0–137)	0.62§
Time to pregnancy >1 year, no. (%)¶	38 (31.7)	56 (29.8)	0.72†

* Values are the total no./no. (%) unless indicated otherwise. RA = rheumatoid arthritis; SpA = spondyloarthritis.
† By Pearson's chi-square test.
‡ By Independent samples *t*-test.
§ By log rank test.
¶ Including women not achieving pregnancy.
# Among women achieving pregnancy having gone through the entire pregnancy.

Women with axial SpA reported considerable pain and low vitality preconception, with a mean SF-36 bodily pain score of 55.1 and a mean SF-36 vitality score of 46.3. However, we found no significant differences in self-reported HRQoL between subfertile and fertile women with axial SpA. Subfertile women with RA were also older and more often nulliparous; otherwise, there were no differences compared to fertile women with RA (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24233/abstract).

Table 3. Differences between subfertile and fertile women with axial spondyloarthritis*

Variable	Subfertility†		
	Yes (n = 58)	No (n = 216)	*P*
Age, years (n = 274)	32.2 ± 5.6	30.3 ± 4.6	0.022‡
Nulliparity, % (n = 272)	38 (65.5)	91 (42.5)	0.002§
Smoking, % (n = 264)	9 (15.8)	8 (3.8)	0.003§
Duration, years (n = 236)	7.3 ± 5.3	4.6 ± 4.1	0.001‡
BMI, kg/m^2 (n = 261)	25.1 ± 4.9	25.1 ± 4.5	0.96‡
BASDAI score (n = 188)	2.9 ± 1.8	3.4 ± 2.3	0.22‡
Mental health (n = 101)	72.8 ± 14.4	75.5 ± 15.1	0.40‡
Vitality (n = 100)	48.3 ± 19.9	45.2 ± 23.3	0.51‡
Bodily pain (n = 102)	54.4 ± 25.3	55.5 ± 23.5	0.83‡
Physical function (n = 101)	80.9 ± 19.3	79.6 ± 18.5	0.75‡
NSAIDs, % (n = 129)	10 (26.3)	28 (30.8)	0.61§
Prednisolone, % (n = 127)	1 (2.6)	4 (4.5)	1.00¶
Methotrexate, % (n = 271)	4 (7.0)	12 (5.6)	0.75¶
TNFi, % (n = 271)	32 (56.1)	101 (47.2)	0.23§

* Values are the mean ± SD unless indicated otherwise. BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BMI = body mass index; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor.
† Time to pregnancy >12 months.
‡ By Independent samples *t*-test.
§ By Pearson's chi-square test.
¶ By Fisher's exact test.

Variables associated with TTP. Cox regression analyses showed that older age, longer disease duration, and nulliparity were associated with longer TTP in the total axial SpA population (Table 4). Longer disease duration and nulliparity were still associated with longer TTP after adjusting for age, with pregnancy ratios of 0.95 (95% confidence interval [95% CI] 0.92–0.99) and 0.62 (95% CI 0.47–0.82), respectively. Women who smoked had a pregnancy ratio of 0.77, but the association was not statistically significant. Scores of the BASDAI or HRQoL were not significantly associated with TTP. Preconception use of NSAIDs, prednisolone, MTX, or TNFi were not significantly associated with TTP.

In the total RA population, younger age, multiparity, and MTX use preconception were associated with shorter TTP (see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24233/abstract). Cox regression analyses including only women enrolled preconception did not show a significant association between nulliparity and longer TTP. Apart from this, results were substantially the same (see Supplementary Tables 3 and 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24233/abstract). Fertility outcomes in axial SpA were comparable to those in RA.

Fertility outcomes in axial SpA compared to RA. As shown in Table 2, subfertility was more common in women with RA when including the total study population while more common in axial SpA when considering only the women who were enrolled

Table 4. Cox regression analyses for occurrence of pregnancy in women with axial spondyloarthritis 1 covariate at a time*

Variable	Pregnancy ratio	95% CI	*P*
Age, per year (n = 221)	0.97	0.94–1.00	0.030
Nulliparity (n = 219)	0.66	0.50–0.88	0.004
Smoking (n = 221)	0.77	0.54–1.11	0.16
BMI, per unit (n = 196)	1.01	0.99–1.04	0.37
Duration, per year (n = 221)	0.94	0.91–0.98	0.001
BASDAI score, per point (n = 152)	1.08	0.99–1.18	0.072
Mental health (n = 78)	1.00	0.99–1.02	0.93
Vitality (n = 77)	0.99	0.98–1.00	0.14
Bodily pain (n = 79)	1.00	0.99–1.01	0.29
Physical function (n =78)	0.99	0.98–1.01	0.31
NSAIDs (n = 101)	1.28	0.80–2.04	0.31
Prednisolone (n = 99)	1.91	0.77–4.74	0.17
Methotrexate (n = 220)	0.99	0.55–1.77	0.96
TNFi (n = 220)	0.88	0.67–1.16	0.38

* 95% CI = 95% confidence interval; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BMI = body mass index; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor.

prior to conception. However, differences between diagnostic groups were small and not statistically significant. The Kaplan-Meier plot in Figure 2 shows that median TTP in women with axial SpA was 2 months (95% CI 1.3–2.7) compared to 3 months (95% CI 2.3–3.7) in women with RA, but the difference was not statistically significant (log rank test $P = 0.112$).

DISCUSSION

In this large registry-based study on fertility in axial SpA, we found a median TTP of 4 months in the subgroup of women enrolled when planning a pregnancy. Of these women, 32% were subfertile, defined as attempting to conceive longer than 12 months. In the total study population, where approximately one-half were already pregnant at enrollment, the median TTP was 2 months, and 21% were subfertile. Longer TTP was related to older age, nulliparity, and longer disease duration. There were no significant differences between women with axial SpA and women with RA in fertility-related outcomes.

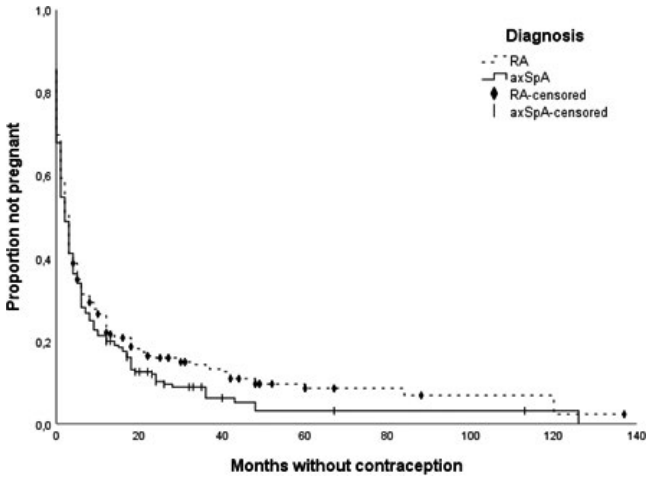

Figure 2. Kaplan-Meier plot for time to pregnancy in women with axial spondyloarthritis (axSpA) compared to women with rheumatoid arthritis (RA).

To our knowledge, this is the first study on TTP in women with axial SpA. A Norwegian study demonstrated a lower fertility rate in women with RA and in a group of women with SpA or unspecified arthritis compared to healthy peers (2).

A study from 1999 showed a prevalence of subfertility of 16% in a general Western European population and a median TTP of 3 months (15). A later study based on population surveys from 25 countries found a mean prevalence of subfertility of 9% (4). In this setting, subfertility appears to be more common in women with axial SpA despite a median TTP similar to that of the general population. However, for direct comparison to the general population, we should have included a healthy control group.

The associations between subfertility and the factors older age, nulliparity, and smoking are well known (16–18). Lack of statistical power may explain why we did not find a significant association between nulliparity and longer TTP in the subgroup that was enrolled preconception. We have no reason to believe that the association between parity and fertility is different in women with axial SpA planning their pregnancy than in healthy women. Mean age and frequency of smoking in the study population were similar to mean maternal age at time of childbirth and the frequency of smoking in early pregnancy in the general Norwegian population (19). Thus, these factors do not seem to explain why subfertility is more common in women with axial SpA. Contrary to what is reported for the general population (20), we did not find an association between a high BMI and longer TTP. It is possible that some women struggling to conceive intentionally lose weight in order to improve fertility, diluting a negative association between a high BMI and fertility.

In the current study, the only disease-related factor associated with longer TTP was disease duration. This association has not been demonstrated in RA or systemic lupus erythematosus (5,7). Studies have shown reduced levels of anti–müllerian hormone (an indicator of ovarian reserves) in women with AS and RA compared to healthy controls (21,22). One study showed that HLA–B27 positivity was associated with lower anti–müllerian hormone (21). Whether some aspect of the pathophysiology of axial SpA over time affects fertility via reduced ovarian reserves or other biologic mechanisms is not known.

The current study confirmed previous findings of poor self-reported HRQoL with regard to vitality and pain in women with axial SpA and RA (7,23). Studies have shown an association between HRQoL and sexuality in women with axial SpA (24,25). We found no association between HRQoL and TTP that could explain an increased prevalence of subfertility.

In the current study, ~19% of women with axial SpA experienced pregnancy loss, compared to ~15% reported in the general

population (26,27). However, in order to study the risk of pregnancy loss in axial SpA, we need population-based case–control studies.

Regarding RA, we found that TTP exceeded 12 months in 24% of the total study population and 30% of the women enrolled preconception. In accordance with our study, a retrospective TTP study by Jawaheer et al found subfertility in 25% of women with RA (6). This study included a healthy control group and was able to demonstrate significantly longer TTP in women with RA. In the Dutch PARA cohort, Brouwer et al found a higher occurrence of subfertility; 42% of 245 women with RA had TTP exceeding 12 months (5). Brouwer et al demonstrated that TTP was associated with age, nulliparity, disease activity, and preconception use of NSAIDs or prednisolone. Similar to the current study, the PARA study had the combination of a prospective and retrospective design; 25% of women were pregnant at inclusion. There are several possible reasons for different findings regarding subfertility. The PARA study was conducted before 2008, while we included women until 2018. Only 15% of the women in the PARA cohort had ever used a biologic disease-modifying antirheumatic drug, while in our study 44% used TNFi in the last year before pregnancy. Additionally, our population had lower disease activity, with a mean DAS28-CRP score of 2.6 versus 3.6 in the PARA cohort.

The low disease activity in our study population, both in RA and axial SpA, may also explain why we found no association between disease activity and TTP. Our previous study of women with axial SpA in RevNatus revealed no significant difference between preconception BASDAI score and first trimester BASDAI score (28). Thus, we do not think that using the first trimester BASDAI score where the preconception score was missing relevantly affected our results.

One reason why we did not find associations between TTP and the use of NSAIDs or prednisolone may be that few women in our study population used prednisolone or NSAIDs continuously. Also, women struggling to conceive might have discontinued NSAIDs in order to facilitate pregnancy, diluting a possible adverse effect of NSAIDs on fertility. Reassuringly, we found no association between preconception TNFi and TTP.

Surprisingly, we found that MTX preconception was associated with shorter TTP in women with RA. Animal studies have suggested a harmful effect of MTX on ovarian reserve (29). In the PARA cohort, there was no association between MTX and TTP (30). We found no known variables explaining why women with RA using MTX preconception had shorter TTP in our study; age, disease duration, and disease activity did not differ significantly compared to those of women not using MTX. We can only speculate about reasons for the association. Women on MTX could have had stable disease activity for a longer period of time before deciding to get pregnant, which may have improved fertility. It is also possible that women who discontinue MTX because they desire to become pregnant have more concrete pregnancy plans and are therefore more aware of the importance of frequency and timing of intercourse.

Fertility is a complex biologic process involving gametogenesis, sperm transport, tubal patency, hormonal preparation of the endometrium, implantation, and the viability of the embryo. In addition, there are several psychosocial and cultural factors involved. Although they only tell part of the story, studies on TTP have proved useful in identifying factors with adverse effects on fertility (31,32).

Retrospectively studying TTP in a group of women who have achieved pregnancy does not yield the same data as prospectively studying TTP in a group of women trying to conceive. In the former group, the sampling unit is the pregnancy, while in the latter the sampling unit is the attempt to become pregnant. In the current study, we used a combination of prospective and retrospective approaches. The main strength of the prospective approach is that it also includes infertile women. In addition, in prospective studies of TTP, it is possible to address underlying biologic processes. However, since RevNatus was not originally designed for studying fertility, we did not have information on ovulation, factors associated with male fertility, or frequency and timing of intercourse.

TTP studies that only include women who are already pregnant may be affected by right truncation bias so that women with longer TTP tend not to be included. Although excluding infertile women and underrepresenting subfertile women, the retrospective approach offers complimentary knowledge. This approach may include unplanned pregnancies not represented in a prospective study. Although telling less about fertility in a strictly biologic sense, studying the total population of women with axial SpA enrolled in RevNatus gives us useful knowledge on how long it takes for women with axial SpA to achieve pregnancy in a real-life setting. Generally, populations in retrospective TTP studies are considered more representative of the target population (32).

Despite being retrospective, recall bias is minimal in TTP studies where the study population is comprised of pregnant women (32). However, this design may cause other types of bias (32). We already mentioned 2 examples of possible behavior change bias: losing weight and discontinuing NSAIDs in order to achieve pregnancy in women struggling to conceive. It is not possible to examine whether our study was affected by planning bias because information on the planning of pregnancy was not recorded in RevNatus before 2016. In the current study, we included all women with TTP of 0 months regardless of pregnancy being planned or unplanned. We do not suspect pregnancy recognition bias. We included miscarriages, but the timing of recognition of pregnancy did not differ according to diagnoses or other relevant variables.

We do not suspect medical intervention bias. Fertility treatment was more common in women with RA than in women with axial SpA, but TTP in women referred to fertility treatment was comparable between diagnoses, showing no tendency for earlier referral of women with RA. When censoring TTP at 14 months in women receiving fertility treatment, as recommended by Joffe et al (32), the median TTP in both diagnoses was the same as in the original analyses. Left truncation bias, resulting in women with relatively shorter TTP not being included, is of particular importance

when studying time trends. We do not suspect left truncation bias in the current study.

The main strength of this study is the large study population, where the majority fulfilled the ASAS criteria. In Norway, the majority of pregnant women with inflammatory rheumatic diseases are followed in the public specialist health care system and enrolled in RevNatus, which makes the registry representative of the population at large. However, there are limitations to generalizability. We cannot exclude that the healthiest women with axial SpA are followed in general practice and thus less likely to be enrolled in RevNatus. On the other hand, some women with axial SpA with high disease activity may never feel healthy enough for pregnancy and will therefore never be enrolled in RevNatus.

Our study would have been strengthened by considering the possible effects of SpA comorbidities. While little is known about fertility and psoriasis, subfertility has been related to disease activity in inflammatory bowel disease (33). However, in the current study, the subpopulations with psoriasis or inflammatory bowel disease were too small for analyses with sufficient statistical power.

In conclusion, women with axial SpA had an occurrence of subfertility surpassing the occurrence demonstrated in the general population. Longer TTP was associated with older age, nulliparity, and longer disease duration. Our findings suggest that women with stable axial SpA should be encouraged not to postpone pregnancy.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Drs. Ursin and Wallenius had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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