RMD Open
Rheumatic & Musculoskeletal Diseases

SHORT REPORT

Low prevalence of anti-SSA (anti-Ro) and anti-SSB (anti-La) autoantibodies in female patients with rheumatoid arthritis with a wish to conceive

Hieronymus T W Smeele ,[1] Marco W J Schreurs,[2] Nathalie Costedoat-Chalumeau,[3] Jerome M J Cornette,[4] Radboud J E M Dolhain[1]

To cite: Smeele HTW, Schreurs MWJ, Costedoat-Chalumeau N, *et al*. Low prevalence of anti-SSA (anti-Ro) and anti-SSB (anti-La) autoantibodies in female patients with rheumatoid arthritis with a wish to conceive. *RMD Open* 2021;**7**:e001727. doi:10.1136/rmdopen-2021-001727

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2021-001727).

This work was previously presented at the EULAR 2021 virtual congress (POS0541).

Received 5 May 2021
Accepted 30 June 2021

For numbered affiliations see end of article.

Correspondence to
Hieronymus T W Smeele;
h.smeele@erasmusmc.nl

ABSTRACT

Objectives Guidelines advise to test for anti–Sjögren's-syndrome-related antigen A (anti-SSA) and anti–Sjögren's-syndrome-related antigen B (anti-SSB) antibodies in all patients with rheumatoid arthritis (RA) who wish to conceive. Our objective was to determine the prevalence and titres of anti-SSA and anti-SSB autoantibodies in patients with RA with a wish to conceive or pregnant.

Methods Patients were derived from two large cohorts on RA and pregnancy (PARA cohort and PreCARA cohort). In addition, to determine the clinical relevance of searching for anti-SSA and anti-SSB in patients with RA, we studied the prevalence of the maternal diagnosis of RA in the French national registry of neonatal lupus syndrome (NLS) and congenital heart block (CHB).

Results 26 out of 647 patients with RA had detectable anti-SSA and/or anti-SSB. Anti-SSA was detected in 25 out of 647 patients (3.9%) (Ro-52, n=17; Ro-60, n=19), anti-SSB in 7 out of 647 (1.1%). Thirteen women had a titre of >240 units/mL of anti-SSA antibodies. The prevalence of anti-SSA and/or anti-SSB was higher in rheumatoid factor (RF)-positive patients compared with RF-negative patients (5.1% vs 1.6%, p=0.04). No cases of CHB and/or NLS in the offspring were observed. In the French national register, the prevalence of RA in mothers with SSA related CHB was 1.5%.

Conclusion Anti-SSA and anti-SSB have a low prevalence in patients with RA who wish to conceive. Especially for RF-negative patients, the current advise to test for anti-SSA and anti-SSB should be reconsidered.

Key messages

What is already known about this subject?

- The presence of maternal anti–Sjögren's-syndrome-related antigen A (anti-SSA) and anti–Sjögren's-syndrome-related antigen B (anti-SSB) autoantibodies is associated with congenital heart block and neonatal lupus syndrome.
- Current American College of Rheumatology(ACR) guidelines on the management of rheumatic diseases during the reproductive period recommend to test for anti-SSA and anti-SSB antibodies in all patients with rheumatoid arthritis with a wish to conceive.

What does this study add?

- Women with rheumatoid arthritis in their reproductive age have a low prevalence and low titres of anti-SSA and anti-SSB antibodies. In particular in rheumatoid factor-negative patients, anti-SSA and anti-SSB autoantibodies are uncommon.
- The prevalence of rheumatoid arthritis in mothers with anti-SSA-related congenital heart block is 1.5%.

How might this impact on clinical practice or future developments?

- If our findings can be replicated in other cohorts, it is justified to critically review the current guidelines on testing for anti-SSA and anti-SSB autoantibodies in women with rheumatoid arthritis. Especially for rheumatoid factor-negative patients with a wish to conceive, the current advise to test for anti-SSA and anti-SSB could be reconsidered.

INTRODUCTION

Anti–Sjögren's-syndrome-related antigen A (anti-SSA oranti-Ro, including Ro-52 kDa and Ro-60 kDa subunits) and anti–Sjögren's-syndrome-related antigen B (anti-SSB oranti-La) autoantibodies are frequently reported in patients with systemic lupus erythematosus (SLE) and Sjögren syndrome (SS).[1]

The association between maternal levels of anti-SSA autoantibodies and complete congenital heart block (CHB) and neonatal Lupus syndrome (NLS) is well established, with CHB occurring in 1%–2% of fetuses exposed to anti-SSA.[1] Moreover, the level of maternal antibodies is associated with fetal complications; higher levels of anti-SSA correlate with a higher risk of cardiac complications whereas pre-natal exposure to high titres of anti-SSB is associated with non-cardiac features of NLS.[2] Intensive preventive

echocardiographic screening strategies have been developed for high-risk women to detect conversion to a CHB in early stage, however, their usefulness is currently questioned.[3]

Nevertheless, the '2020-ACR-Guideline-for-the-Management-of-Reproductive-Health-in-Rheumatic-and-Musculoskeletal-Diseases' recommends to screen for anti-SSA and anti-SSB in all patients with rheumatoid arthritis (RA) who are planning pregnancy or who are pregnant.[4] Hence, highlighting the importance of knowledge on the prevalence of anti-SSA and anti-SSB in this patient group. Until now, no studies on the presence of these autoantibodies in patients with RA in the reproductive age have been published.

The objective of this study is to determine the prevalence and titres of anti-SSA and anti-SSB autoantibodies in patients with RA and a wish to conceive and to determine the clinical relevance of searching for anti-SSA and anti-SSB in patients with RA by analysing the prevalence of the maternal diagnosis of RA in the French national registry of NLS and CHB.

METHODS

Population

Participants were derived from two cohort studies on RA and pregnancy: PARA-cohort[5] and the ongoing PreCARA-cohort.[6] These studies were approved by the Erasmus MC ethics review board in compliance with the Helsinki declaration. All patients with RA were over 18 years of age and gave informed consent.

Data collection

Study procedures for both PARA and PreCARA cohorts are extensively described previously.[6 7] Blood was collected at every visit, serum samples were stored at −80°C.

The presence and titres of anti-SSA (both Ro-52 kDa and Ro-60 kDa subunits) and anti-SSB were quantitatively determined by fluorescence-enzyme immunoassay (FEIA) using EliA technology on the Phadia-250 system according to manufacturer's instructions (Thermo Fisher Scientific, Freiburg, Germany). The upper limit of quantification for this test is >240 units/mL for anti-SSA and >340 units/mL for anti-SSB. Normal range for both antibodies is <7 units/mL.

In a previous study on maternal anti-SSA antibodies as a prognostic marker, ELISA was used to determine these antibodies.[2] To allow quantitative comparison of our anti-SSA FEIA results with the anti-SSA ELISA results, we determined a conversion factor between both assays.

Statistical analyses

Descriptive statistics are shown as numbers (n) and percentages (%). Values are presented as mean±SD or median±IQR. Categorical data were tested using Fisher's-exact or χ^2 tests, continuous data were tested using Student's t-test or Wilcoxon-rank. A two-sided p value of <0.05 was considered significant. All statistical analyses were performed using Stata V.16 (StataCorp-LP).

Maternal diagnosis of auto-immune disease in fetuses with CHB

To determine the clinical relevance of anti-SSA and anti-SSB in patients with RA, data of the French national registry of NLS and CHB were obtained. The data include fetuses or children born to mothers with anti-SSA and/or anti-SSB antibodies and were previously published by Levesque *et al*.[8] In this cohort, we studied the prevalence of a maternal diagnosis of RA among all maternal diagnoses of an autoimmune disease.

RESULTS

Twenty-six out of six hundred and forty-seven patients with RA with a wish to conceive had detectable anti-SSA and/or anti-SSB antibodies: anti-SSA was detected in 25 (3.9%) (Ro-52 n=17, Ro-60 n=19), anti-SSB in 7 patients (1.1%). Table 1 shows a detailed description of the study population stratified for the presence of anti-SSA and/or anti-SSB. The prevalence anti-SSA and/or anti-SSB was higher in rheumatoid factor (RF)-positive patients compared with RF-negative patients (5.1% vs 1.6%, p=0.04). This observation was not seen for anti–citrullinated protein antibody(ACPA) (p=0.99).

Table 1 Clinical and demographic features from 647 women with rheumatoid arthritis and a wish to conceive stratified for the presence of anti-SSA and/or anti-SSB antibodies

Variable	Anti-SSA and anti-SSB antibodies negative, n=621	Anti-SSA and/or anti-SSB antibodies positive, n=26	P value
Age at inclusion in the cohort (years, SD)	32.3 (4.0)	32.3 (4.3)	0.91
Median disease duration at first visit, years (IQR)	5.2 (2.2–9.8)	4.4 (1.8–11.4)	0.96
ACPA positive, n (%)	408/613 (66.6)	16/24 (66.7)	0.99
Rheumatoid factor positive, n (%)	426/616 (69.0)	23/26 (88.5)	0.04
Nulliparity, n (%)	335/621 (54.0)	16/26 (61.5)	0.45
Erosive disease, n (%)	241/621 (38.8)	14/26 (53.9)	0.12

ACPA, Anti–citrullinated protein antibody; anti-SSA, anti–Sjögren's-syndrome-related antigen A; anti-SSB, anti–Sjögren's-syndrome-related antigen B.

Table 2 Prevalence and titres of anti-SSA and/or anti-SSB antibodies in patients with RA with a wish to conceive (total number of inclusions=647)

	Number of patients (%)	Prevalence (%)	Titre of antibodies (units/mL) (median, range)
Anti-SSA antibodies (combined 52 kDa and 60 kDa subunits)	25	3.9	29.0 (7–159)
Anti-SSA antibodies titres 0–240 units/mL	12 (48.0)	1.9	
Anti-SSA antibodies above detection limit (>240 units/mL)	13 (52.0)	2.0	
Anti-SSB antibodies	7	1.1	18.8 (8.5–142)
Anti-SSB antibodies titres 0–340 units/mL	4 (57.1)	0.6	
Anti-SSB antibodies above detection limit (>340 units/mL)	3 (42.9)	0.5	

Titres of anti-SSA and anti-SSB antibodies

Thirteen (52% of the anti-SSA positive patients, 2.0% of the total population) patients had a titre of >240 units/mL of anti-SSA antibodies (table 2). Three (42.9% of the anti-SSB positive patients, 0.46% of the total population) patients had titres >340 units/mL, two of these patients had combined anti-SSA titres of >240 units/mL, the titre of anti-SSA in the remaining patient was 159 units/mL. One patient only had anti-SSB antibodies, and no anti-SSA. The titre of anti-SSB in this patient was 8.5 units/mL.

CHB and NLS

No cases of CHB or NLS were observed in the PARA and PreCARA cohort.

Maternal diagnosis of RA in fetuses with congenital atrioventricular block in the French national registry of NLS and CHB

Fifty-one out of one hundred and ninety-five mothers (26.3%, 1 missing data) with CHB in the French national registry of NLS and CHB had a diagnosis of autoimmune disease. Three (1.5% of the total population, 5.9% of the patients with an autoimmune disease) of these women had RA. One patient with RA (unknown RF and/or ACPA status) had an overlap-syndrome with SLE. The other two had an isolated diagnosis of RA (one patient: unknown RF and/or ACPA status, the other patient RF positive, ACPA status unknown). None of the cases of NLS within this cohort were born to mothers with RA.

Conversion factor between current FEIA and previous ELISA to determine anti-SSA antibodies

A conservative conversion factor of 3.2 between both anti-SSA assays was determined (online supplemental figure 1).

DISCUSSION

In this first article on the presence of anti-SSA and anti-SSB in women with RA in their reproductive age, we showed that the prevalence of these antibodies in this patient population is low. The prevalence of these antibodies was higher in RF-positive patients compared with RF-negative patients.

We observed a lower prevalence of anti-SSA in patients with RA compared with previous studies. A study by Cavazzana *et al* (n=195) observed a prevalence of anti-SSA of 6%[9] in patients with RA, differences in patients characteristics like, higher age and increased coexisting SS/SLE are most likely attributing to this observation. Although anti-SSA is probably the most prevalent autoantibody found in the general population, data are scarce[10]: in a Japanese study, 58/2181 (2.7%) healthy residents had detectable anti-SSA antibodies.[11] Their observed prevalence of anti-SSA is only slightly lower to that we observed in the total RA population in the current study (3.9%), and comparable to what we observed in RF-negative patients (1.6%).

The occurrence of CHB in the presence of anti-SSA is depended on the titre of these antibodies. Jaeggi *et al* showed that women with low anti-SSA antibody titres have almost no risk of CHB and only antibody titres of >100 units/mL are clinically relevant.[2] Our observed titres cannot be compared with the titres observed by Jeaggi *et al* directly, since we used a different quantification method. We compared both quantification methods (online supplemental figure 1), the proposed 'high titres' of 100 units/mL as measured by ELISA probably best correspond with the upper detection limit of >240 units/mL in FEIA. Therefore, the prevalence of patients with clinically relevant titres of anti-SSA is probably around 2%.

To determine the clinical relevance of anti-SSA and/or anti-SSB in patients with RA, we showed that in the French CHB register, only 1.5% of all cases were observed in women diagnosed with RA. This observation was in line with previous literature, in which no maternal diagnosis of RA in children born with congenital cardiac manifestations related to anti-SSA were observed.[12]

Almost all patients that have anti-SSB antibodies have concomitant anti-SSA antibodies,[1] an observation which is confirmed in our study. The role of anti-SSB-antibodies in the development of CHB is uncertain, most literature suggests that the development of immune mediated CHB is associated to fetal exposure to high titres of anti-SSA,

whereas the presence of anti-SSB may not be required.[2] Taking into account both this insight and the low observed prevalence of anti-SSB in patients with RA with a wish to conceive, testing for anti-SSB antibodies in patients, as advised by current guidelines, might not be appropriate.

Intensive surveillance in patients with anti-SSA antibodies has been the dogma for decades. However, CHB is rarely discovered and if so, there is no known effective therapy for CHB, especially since fluorinated steroids failed to demonstrate their efficacy.[3 13] Consequently, the 2016 EULAR recommendations on pregnancy and SLE/APS stated that the cost-effectiveness of intensive surveillance with fetal echocardiography in patients with anti-SSA and anti-SSB and no previous child with CHB remains to be established.[14] They also recommended against performing systematic fetal echocardiography but only to do so in cases of suspected fetal dysrhythmia or myocarditis.[14] We showed a low prevalence of anti-SSA in patients with RA with a wish to conceive. Therefore, even if these antibodies were to be detected the consequences are more than uncertain.

Some limitations need to be considered, due to the low number of patients with detectable anti-SSA and/or anti-SSB, we were unable to test associated factors with these antibodies in a multivariate analysis. And, total antinuclear antibody titres and titres of ACPA and RF were not available. Furthermore, due to the absence of CHB in our cohort of patients with RA we were unable to determine valuable clinical cut-off points for anti-SSA titres in patients with RA. Based on the nature of this condition, scientific consensus on testing can only be achieved by replicating our results in other study populations.

In conclusion, anti-SSA and anti-SSB have a low prevalence in patients with RA with a wish to conceive. Moreover, in the French national registry of NLS and CHB maternal diagnosis of RA was infrequent. If our findings could be replicated in other studies, it is justified to critically review the current guidelines. Especially since the practical consequences of finding these antibodies is currently questioned. In particular for RF-negative patients the current advise to test for both anti-SSA and anti-SSB can be reconsidered.

Author affiliations
[1]Rheumatology, Erasmus Medical Center, Rotterdam, The Netherlands
[2]Department of Immunology, Erasmus Medical Center, Rotterdam, The Netherlands
[3]Hôpital Cochin, Centre de Référence Maladies Auto-immunes et Systémiques Rares, Paris, France
[4]Department of Obstetrics and Fetal medicine, Erasmus Medical Center, Rotterdam, The Netherlands

Acknowledgements We thank all participants of the PreCARA and PARA studies. Additionally, we extend our gratitude to the laboratory workers, in particular Nadine Davelaar and Priyanka Bangoer, and research assistants for their contribution to the data collection. We thank ReumaNederland (LLP project number: LLP-26) for their financial support. The kits for measurement of anti-SSA and anti-SSB were a kind gift from Thermo Fischer Scientific. We also thank Thermo Fischer Scientific for providing the original results of the anti-SSA FEIA versus ELISA comparison.

Contributors All authors met the authorship criteria, they had a substantial contribution to the conception or design of the work (HS, MWJS, JMJC, RJEMD) or the acquisition (MWJS, RJEMD, NC-C), analysis (HS, RJEMD) or interpretation of data for the work (all authors) and were involved in revising a draft of this work, gave final approval of this version to be published and are accountable for all aspects of the work in ensuring accuracy and integrity.

Funding This work was supported by the Dutch Arthritis Foundation (ReumaNederland) (project number: LLP-26). The kits for measurement of anti-SSA and anti-SSB were a kind gift from Thermo Fischer Scientific.

Competing interests None declared.

Patient and public involvement statement Patients were involved in the design of the PARA and PreCARA cohorts. We obtained input from patients in the design of the questionnaires, materials and management. We carefully assessed the burden on participating patients and intend to share the results to participating patients.

Patient consent for publication Obtained.

Ethics approval Approval obtained (MEC-214.320/2002/117 and MEC-2011-032).

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Hieronymus T W Smeele http://orcid.org/0000-0001-7724-7712

REFERENCES

1 Brito-Zerón P, Izmirly PM, Ramos-Casals M, *et al*. The clinical spectrum of autoimmune congenital heart block. *Nat Rev Rheumatol* 2015;11:301–12.
2 Jaeggi E, Laskin C, Hamilton R, *et al*. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus a prospective study of 186 antibody-exposed fetuses and infants. *J Am Coll Cardiol* 2010;55:2778–84.
3 Costedoat-Chalumeau N, Morel N, Fischer-Betz R, *et al*. Routine repeated echocardiographic monitoring of fetuses exposed to maternal anti-SSA antibodies: time to question the dogma. *Lancet Rheumatol* 2019;1:e187–93.
4 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 Care Res* 2020;72:461–88.
5 de Man YA, Hazes JMW, van de Geijn FE, *et al*. Measuring disease activity and functionality during pregnancy in patients with rheumatoid arthritis. *Arthritis Rheum* 2007;57:716–22.
6 Smeele HT, Röder E, Wintjes HM, *et al*. Modern treatment approach results in low disease activity in 90% of pregnant rheumatoid arthritis patients: the PreCARA study. *Ann Rheum Dis* 2021;80:859–64.
7 de Man YA, Dolhain RJEM, van de Geijn FE, *et al*. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum* 2008;59:1241–8.
8 Levesque K, Morel N, Maltret A, *et al*. Description of 214 cases of autoimmune congenital heart block: results of the French neonatal lupus syndrome. *Autoimmun Rev* 2015;14:1154–60.
9 Cavazzana I, Franceschini F, Quinzanini M, *et al*. Anti-Ro/SSA antibodies in rheumatoid arthritis: clinical and immunologic associations. *Clin Exp Rheumatol* 2006;24:59–64.
10 Guo Y-P, Wang C-G, Liu X, *et al*. The prevalence of antinuclear antibodies in the general population of China: a cross-sectional study. *Curr Ther Res Clin Exp* 2014;76:116–9.
11 Hayashi N, Koshiba M, Nishimura K, *et al*. Prevalence of disease-specific antinuclear antibodies in general population: estimates from annual physical examinations of residents of a small town over a 5-year period. *Mod Rheumatol* 2008;18:153–60.
12 Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, *et al*. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. *Circulation* 2012;126:76–82.
13 Brucato A, Cimaz R, Caporali R, *et al*. Pregnancy outcomes in patients with autoimmune diseases and anti-Ro/SSA antibodies. *Clin Rev Allergy Immunol* 2011;40:27–41.
14 Andreoli L, Bertsias GK, Agmon-Levin N, *et al*. EULAR recommendations for women's health and the management of family

planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis* 2017;76:476–85.