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Systematic review and meta analysis

Risk of adverse pregnancy outcomes prior to the onset of an autoimmune rheumatic disease: a systematic review

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Abstract

Objectives. An increased risk of adverse maternal and foetal pregnancy complications (including pre-eclampsia, intrauterine growth restriction, and small for gestational age) is well described in women with autoimmune rheumatic disease (ARD) compared with the general population (GenPop). It is less clear, however, whether this risk of adverse pregnancy outcome (APO) also exists in women with 'preclinical ARD' (pre-ARD) before they are diagnosed with an ARD many years post-partum. Therefore, we have undertaken a systematic review of the available evidence on APO in patients who subsequently were diagnosed with a rheumatic disease to identify whether there is an increased risk in pre-ARD.
Methods. The present study was reported in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard. A systematic literature review was performed using the online PubMed database. Pre-SLE and pre-RA patients were defined as those who, over the subsequent years, developed SLE or RA according to international classification criteria.
Results. A total of 176 articles were screened, and 27 original articles were selected for final analysis. Pre-RA was the most studied group, with 15 studies and a total of >1600 pregnancies, and pre-SLE was the second-most studied pre-ARD in pregnancy, with 14 studies and a total of >1000 pregnancies. We found that patients who subsequently developed SLE had an increased burden of poor pregnancy outcomes compared with pregnant women from the GenPop, but fewer APOs compared with pregnancies of women with SLE. In contrast, a similar rate of APOs was found when pre-RA pregnancies were compared with GenPop pregnancies.
Conclusion. Our findings of an increased risk of APO in certain pre-ARDs highlights the relevance of taking an obstetric history during the first rheumatology appointment and the need for novel screening strategies for the prediction of APOs. Further research is required to elucidate the immune basis of APOs in preclinical and clinical ARD.

Key words: lupus, RA, autoimmune rheumatic disease, adverse pregnancy outcomes, obstetric complications

CLINICAL SCIENCE

Rheumatology key messages

- Pre-SLE and pre-SSc women were found to have an increased risk of adverse pregnancy outcome compared with GenPop women.
- An obstetric history at first review in the Rheumatology clinic would be helpful, especially in the early stages of an autoimmune rheumatic disease (ARD).
- Screening strategies should be considered to predict adverse pregnancy outcomes in patients with initial symptoms of an ARD.

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Introduction

Autoimmune rheumatic diseases (ARDs), including SLE, RA and other inflammatory arthropathies, affect women of childbearing age. An increased burden of adverse pregnancy outcomes (APO) has been reported in various ARDs [1].

This increased risk of APOs is well documented in patients with clinical and laboratory manifestations of disease fulfilling the relevant classification criteria that are commonly used in clinical practice to aid diagnosis, despite such criteria being developed to identify a homogeneous group of patients for research purposes. It is less certain, however, whether a similar risk also exists in patients with preclinical disease. The concept of preclinical rheumatic disease is well established, and it is considered to occur in several stages. These stages include a period of genetic risk, exposure to environmental factors, followed by development of asymptomatic autoimmunity, then non-specific symptoms, elaboration of an immune or inflammatory response, and ultimately, definitive clinical manifestations [2].

Consequently, several studies have examined the incidence of pregnancy complications in women before they fulfilled relevant classification criteria for a rheumatic disease. These studies however, have yielded conflicting findings, with some reporting an increased risk of APOs [3–7] but others finding no increase in risk [8–11].

Therefore, we have carried out this systematic review of the available evidence regarding APOs in patients who subsequently developed a rheumatic disease, to identify whether there was any association between them. Specifically, we aimed to determine whether a preclinical ARD (pre-ARD) is associated with an increased risk of APOs.

Methods

The present study was reported in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard [12]. A systematic literature review was performed using the online PubMed (MEDLINE) database from inception to the beginning of June 2021. Search terms used were different combinations of the key words, as shown in Box 1. This systematic review was registered at PROSPERO in October 2020 under the registration number CRD42021224960.

Inclusion criteria

Relevant articles were those deemed to contain original information about pregnancy outcomes in patients who subsequently developed an autoimmune disease over subsequent years, also called a pre-ARD, including pre-SLE, pre-RA, pre-JIA, pre-SS, pre-SSc, pre-AS, preclinical Still's disease (pre-SD), preclinical palindromic rheumatism (pre-PR), pre-PsA and inflammatory polyarthritis (IPA). Definitions of these terms are listed in Table 1. We selected studies, with or without comparators, of either pregnant women having a suspected autoimmune disease and/or GenPop pregnant women. For studies reporting duplicate populations, the most comprehensive studies with the largest sample size were selected.

Box 1 Search criteria

a. **Disease**
- OR 'lupus' OR 'SLE'
- OR 'rheumatoid arthritis' OR 'RA'
- OR 'inflammatory polyarthritis'
- OR 'Still's disease'
- OR 'ankylosing spondylitis' OR 'AS'
- OR 'psoriatic arthritis'
- OR 'palindromic rheumatism'
- OR 'axial spondyloarthritis'
- OR 'systemic sclerosis' OR 'scleroderma'
- OR 'Sjögren syndrome' OR 'Sjögren's syndrome'

b. **Status**
- OR 'Preclinical'
- OR 'Early onset'
- OR 'Before onset'
- OR 'Subsequent'

c. **Pregnancy**
- OR 'Obstetric'
- OR 'Pregnancy'

d. **Results**
- OR 'Outcomes'

(a) AND (b) AND (c) AND (d)

Exclusion criteria

We excluded articles written in a language other than English or Spanish and those published only as abstracts.

Study selection

Three independent reviewers (C.M., B.G. and K.A.) screened each title and abstract to identify studies that met the inclusion criteria for full-text review. A data extraction sheet was designed, piloted using 5 papers, and then revised to optimize data retrieval. The final report included details of the study design and methodology, type of pre-ARD, number of patients and pregnancies, pregnancy outcomes, and a summary of the most relevant findings in each study. Study limitations were documented. The quality of the evidence was assessed using GRADE methodology [13].

Results

Outcome from systematic search

Of 176 articles initially screened, 27 original articles were selected for final analysis (Fig. 1). They included 16 single-centre, 11 multicentre, 21 retrospective and 6 prospective studies. The pre-ARDs identified in overlapping studies included: 15 × pre-RA; 14 × pre-SLE; 1 × pre-SSc;

Table 1 Definitions of the used terms in this systematic review

Term	Definition
Pre-SLE	Patients who, over subsequent years, developed SLE according to international classification criteria
Pre-RA	Patients who, over subsequent years, developed RA according to international classification criteria
Pre-JIA	Patients who, over subsequent years, developed JIA according to international classification criteria
Pre-SS	Patients who, over subsequent years, developed SS according to international classification criteria
Pre-SSc	Patients who, over subsequent years, developed SSc according to international classification criteria
Pre-AS	Patients who, over subsequent years, developed AS according to international classification criteria.
Pre-AOSD	Patients who, over subsequent years, developed adult-onset Still's Disease (AOSD) according to international classification criteria.
Pre-PR	Patients who, over subsequent years, developed palindromic rheumatism (PR) according to international classification criteria.
Pre-PsA	Patients who, over subsequent years, developed PsA according to international classification criteria.
IPA	Patients with $\geq$2 swollen joints persisting for $\geq$4 weeks [26]. Up to 66% of IPA patients can develop RA in the subsequent 5 years [49]
HC	Pregnant patients without fulfilling criteria for an autoimmune disease
APO	Adverse pregnancy outcomes included were: pre-eclampsia, new-onset hypertension after 20 weeks gestation, and proteinuria; haemolysis elevated liver enzymes and low platelet count (HELLP) syndrome; preterm birth, <37 weeks gestation; recurrent first-trimester pregnancy loss (>2); spontaneous abortion (<20 weeks gestation); stillbirth (>20 weeks gestation); foetal loss (spontaneous abortion plus stillbirth); intrauterine growth restriction (IUGR), below-normal growth; small-for-gestational-age (SGA), birth weight below the 10th percentile for the appropriate gestational age.

2 × pre-SS; 2 × pre-PsA; 1 × pre-JIA; 1 × pre-IPA; and 1 × pre-AS. Numbers of APOs in the pre-ARD group were compared with numbers of APOs in other comparator groups, including GenPop pregnant women (in 20 studies) and pregnant women fulfilling criteria for an ARD (in 15 studies). Two of 27 studies lacked any comparator group. We did not find any articles that met our inclusion criteria for either Still's disease or palindromic rheumatism.

Pregnancy outcomes in preARD patients

We subdivided our analysis of pregnancy outcomes and their association with subsequent ARDs into three groups: pre-SLE, shown in Table 2; pre-RA, shown in Table 3; and other pre-ARDs, shown in Table 4.

Pregnancy outcomes in pre-SLE vs *SLE and GenPop pregnant women*

Fourteen studies examined pregnancy outcomes in mostly single-centre retrospective studies (8/14) with moderate (1/14), low (10/14) or very low (3/14) grades of evidence. While 7/14 of the total were cohort studies, the other seven were case–control studies [3–5, 8, 9, 14–22]. In these studies, pre-SLE pregnancies were compared with GenPop pregnancies in 11 studies and with SLE pregnancies in 10 studies.

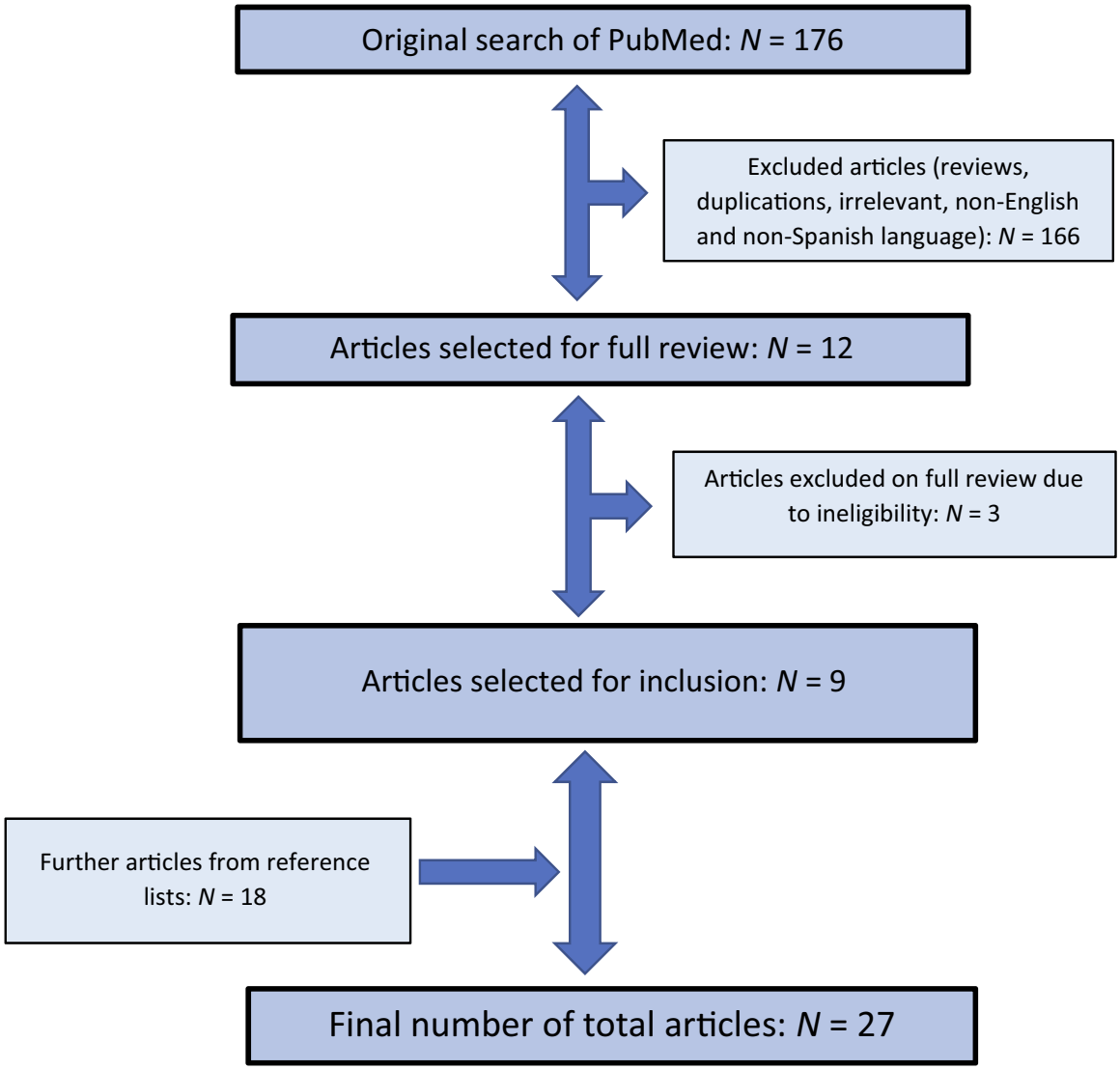
Comparing pre-SLE and GenPop pregnancies, we found the majority (10/11) of the studies with moderate [14] and low [3–5, 8, 9, 15–18] grade of evidence described an increased risk of APOs in the pre-SLE group (Table 2). However, one study [19] with a low grade of evidence did not find significant differences between the groups. Similarly, when comparing SLE and pre-SLE pregnancies, most (7/10) of the collected studies (five with a low [3–5, 8, 15] and two with a very low [20, 21] grade of evidence) found a greater proportion of APOs in the SLE group. While one low-grade-of-evidence study [9] described similar outcomes between SLE and pre-SLE, one other study [22] with a very low grade of evidence reported a higher percentage of APOs in the pre-SLE group than in the SLE group. One moderate-grade-of-evidence study by Arkema *et al.* [14] reported a comparable number of obstetric complications in the SLE group of women and in the group of women who developed the disease within 0–2 years after the pregnancy. However, both groups had a higher risk of APOs than the pre-SLE patients who developed the disease within 2–5 years.

Pregnancy outcomes in pre-RA vs *RA patients and GenPop pregnant women*

Fifteen (5 prospective and 10 retrospective) studies were identified examining pregnancy outcomes in pre-RA patients. While 8/15 were single-centre studies with a low grade of evidence, 7/15 were multicentre studies with a moderate (2/7) or a low (5/7) grade of evidence [6, 7, 9–11, 18, 19, 23–30]. In these studies, pre-RA pregnancies were compared with pregnancies of GenPop pregnant women (in 13 studies) and pregnancies of women with RA (in 2 studies).

Comparing pre-RA and GenPop pregnant women, we found the majority (10/13) of the studies (with a moderate [10, 26] and a low [9, 11, 19, 23–25, 27, 30] grade of evidence) described a similar risk of APOs between the groups (Table 3). However, two studies [6, 18] with a low grade of evidence did find a significant increased risk of APOs in the pre-RA group when compared with GenPop pregnant women, and one study was inconclusive [7]. In addition, when comparing RA and pre-RA pregnancies, two studies [28, 29] with a low grade of evidence found a similar risk of APOs before and after the RA diagnosis.

Fig. 1 Flow diagram of articles selected for final analysis



Pregnancy and maternal outcomes in pre-ARD vs *ARD patients and GenPop pregnant women*

Seven studies examined the impact of other pre-ARDs (including pre-SSc, pre-SS, pre-PsA or pre-JIA) on pregnancies in comparison with pregnancies in GenPop women and/or women with an ARD, with 4/7 being multicentre retrospective, 2/7 single-centre (1 retrospective and 1 prospective) and 1/7 dual-centre retrospective studies. All studies had a low grade of evidence [9, 17–19, 28, 30, 31].

The majority (4/7) of these studies found either a higher risk of subsequently developing an ARD after experiencing an APO, or an increased risk of APO in the pre-ARD group compared with GenPop pregnancies (Table 4). However, 2 studies [9, 30] found a similar rate of APOs when pre-ARD pregnant women were compared with GenPop pregnant women. In addition, 1 study [28] found a similar risk of APOs before and after the RA and PsA diagnoses. All studies were assessed as having a low grade of evidence.

Discussion

Overall, we found evidence suggesting an increased incidence of APOs in pre-SLE but not pre-RA patients when compared with GenPop pregnant women. Fewer studies examined pregnancy outcomes in other pre-ARDs, but the largest study (of 1.5 million pregnancies) reporting a significant increase in APOs in women who subsequently developed various ARDs compared with those who did not.

An increased risk of maternal and foetal morbidity and mortality has been widely described in women with ARDs compared with the GenPop [32–34]. This

Table 2 Data from original studies of pregnancy outcomes in pre-SLE patients

First author	Suspected autoimmune disease	Study design	No. of patients/ pregnancies (pre-ARD/ ARD/controls)	Pregnancy outcomes (pre-ARD/ARD/controls)	Summary of findings	Grade of evidence
Arkema E	SLE	Multicentre prospective study	13 598 patients (551 SLE; 65 pre-SLE to SLE in 0–2 years; 133 pre-SLE to SLE in 2–5 years; 12 847 HCs/13 598 pregnancies (551 SLE; 65 pre-SLE to SLE in 0–2 years; 133 pre-SLE to SLE in 2–5 years; 12 847 HCs)	SLE *vs* pre-SLE (0–2 years) *vs* pre-SLE (3–5 years) *vs* HCs Pec: 16% *vs* 26% *vs* 13% *vs* 5%; PB: 23% *vs* 30% *vs* 16% *vs* 6%; SGA: 14% *vs* 18% *vs* 14% *vs* 3%	Unfavourable maternal and foetal outcomes are observed in pregnancies occurring prior to the diagnosis of SLE	Moderate
Barnardo A	SLE	Single-centre retrospective study	437 patients [220 (pre-SLE + SLE); 217 HC]/1271 pregnancies (pre-SLE: 337; SLE: 147; unknown other: 93; HCs: 694)	Pre-SLE *vs* SLE *vs* HCs APO: 34% *vs* 51% *vs* 19%; SA: 12% *vs* 6.5% *vs* 9%; ST: 2.6% *vs* 3.4% *vs* 0.7%; PB: 9% *vs* 17% *vs* 4%; Pec: 8% *vs* 9.5% *vs* 4%	Increased risk of APOs in both pre-SLE and overt SLE patients compared with controls; the presence of a predisease state that negatively impacts pregnancy outcomes.	Low
Petri M	SLE	Single-centre retrospective study	546 patients [203 (pre-SLE+SLE); 343 HC]/1403 pregnancies [481(pre-SLE+SLE); 922 HCs]	Pre-SLE *vs* SLE *vs* HCs PL (ST+SA+miscarriages): 19% *vs* 27% *vs* 11%; PB: 6% *vs* 24% *vs* 4%	PL and preterm delivery are significantly increased in both pre-SLE and overt SLE pregnancy *vs* controls	Low
Hardy C	SLE	Single-centre retrospective study	414 patients [138 (pre-SLE + SLE); 276 HCs]/929 pregnancies (270 pre-SLE; 47 SLE; 612 HCs)	Pre-SLE *vs* SLE *vs* HCs PL (ST+SA+miscarriages+ ectopic pregnancy): 15% *vs* 23% *vs* 8%	PL was not significantly different between the pre-SLE and SLE groups. However, PL was higher in both *vs* controls, suggesting a higher risk of APOs in lupus women prior to diagnosis.	Low
Dhar P	SLE	Single-centre retrospective study	51 084 patients all with live births (15 pre-SLE; 69 SLE; 51 000 HCs)/51 084 pregnancies (15 pre-SLE; 69 SLE; 51 000 HCs)	Pre-SLE *vs* SLE *vs* HCs PB: 20% *vs* 27% *vs* 15%; LBW: 13% *vs* 28% *vs* 15%; ELBW: 13% *vs* 9% *vs* 4%; SGA: 13% *vs* 10% *vs* 5%	Poor foetal outcomes are seen in pregnancies that are complicated by lupus, even before clinical appearance of disease, which supports a predisease state.	Low
Julkunen H	SLE	Single-centre retrospective study	204 patients [112 (pre-SLE+SLE); 192 HCs]/656 pregnancies (134 pre-SLE; 105 SLE; 417 HCs)	Pre-SLE *vs* SLE *vs* HCs IUGR: 7% *vs* 13% *vs* 1.5%; SA(<22ws): 12% *vs* 19% *vs* 9%; ST: 0% *vs* 2% *vs* 0%; PB: 7% *vs* 27% *vs* 5%	Relative risk of foetal loss, preterm birth and IUGR was greater in overt SLE than before diagnosis and in the control group.	Low

(continued)

Table 2 Continued

First author	Suspected autoimmune disease	Study design	No. of patients/ pregnancies (pre-ARD/ ARD/controls)	Pregnancy outcomes (pre-ARD/ARD/controls)	Summary of findings	Grade of evidence
Johns K	SLE	Single-centre retrospective study	28 patients (pre-SLE+SLE)/ 54 pregnancies (10 pre-SLE; 44 SLE)	Pre-SLE *vs* SLE LB: 70% *vs* 63%; SA: 20% *vs* 30%; ST: 10% *vs* 7.5%	Women with a predisposition to developing SLE have a higher risk of an APO, and this risk increases with clinical disease activity. Mild SLE seems to have better foetal outcomes.	Very low
Kiss E	SLE	Single-centre retrospective study	99 patients (pre-SLE+SLE)/ 263 pregnancies (202 pre-SLE; 61 SLE)	Pre-SLE *vs* SLE LB: 76% *vs* 39%; SA: 2% *vs* 12%; ST: 0.6% *vs* 0%	LB increased in before *vs* after group. However, SAs are more frequent in women with SLE. No differences were found before or after the development of the ARD in terms of stillbirth.	Very low
Kleinman D	SLE	Single-centre retrospective study	21 patients (pre-SLE+SLE)/ 56 pregnancies (pre-SLE+SLE)	Pre-SLE *vs* SLE LB: 46% *vs* 85%; SA: 36% *vs* 10%; ST: 18% *vs* 3%	The percentage of LBs was lower in before *vs* after group; the percentage of SA and ST increased in before *vs* after group.	Very low
Ulff-Moller C	SLE	Multicentre retrospective study	1 390 000 patients (737 pre-SLE; 1 389 263 HCs)/No. of pregnancies NF	Risk of SLE in patients with 1 or more SAs (RR 1.43; 95% CI 1.08, 1.88) compared with those with no previous SA; risk of SLE in patients with 1 or more STs (RR 3.93; 95% CI 1.95, 6.96) compared with those without previous ST; risk of SLE in patients with 1 or more missed abortions (RR 2.13; 95% CI 1.48, 2.98) compared with those without a past missed abortion	Women who experienced SA, missed abortions, or ST are at increased SLE risk	Low

Pre-SLE: SLE before the onset; HC: healthy control; APO: adverse pregnancy outcome; LB: live birth; PB: preterm birth; SA: spontaneous abortion; ST: stillbirth; PL: pregnancy loss (SA+ST); Pec: pre-eclampsia; IUGR: intrauterine growth restriction; LBW: low birth weight; ELBW: extreme low birth weight; NF: not found.

Table 3 Data from original studies of pregnancy outcomes in patients with RA and other inflammatory arthropathies

First author	Suspected autoimmune disease	Study design	No. of patients (pre-ARD/ARD/controls)/pregnancies	Pregnancy outcomes (pre-ARD/ARD/control pregnancies)	Summary of findings	Grade of evidence
Ma K	RA	Multicentre retrospective study	1304 patients (202 pre-RA; 1102 HCs)/1304 pregnancies (202 pre-RA; 1102 HCs)	Pre-RA *vs* controls LBW: 18% *vs* 14%; ELBW: 2% *vs* 1%; PB: 17% *vs* 13%	Prior LBW deliveries and preterm births were more common among pre-RA cases than controls, but the differences were not statistically significant. There is a higher risk of RA among parous women after delivery of an extremely small neonate as compared with delivery of a normal-birth-weight infant	Low
Kay A	RA	Single-centre prospective study	418 patients [premenopausal onset RA (PRE): 98 RA/98 HCs; postmenopausal onset RA(POST): 111 RA/111 HCs]/pregnancies: PRE (156 RA/240 HCs)/POST (172 RA/235 HCs)	PREmenopausal onset RA *vs* HCs LB: 82% *vs* 90%; SA: 16% *vs* 9%; ST: 2% *vs* 0.4% POSTmenopausal onset RA *vs* HCs LB: 90% *vs* 86%; SA: 8% *vs* 11%; ST: 2% *vs* 2.5%	Not clear association between APO and a subsequent development of RA	Low
Silman AJ	RA	Single-centre retrospective study	107 patients (40 RA+pre-RA; 67 HCs)/295 pregnancies (113 RA+pre-RA; 182 HCs)	RA *vs* HCs ST: 6% *vs* 0.5%; SA: 11% *vs* 8%	All the stillbirths in the RA/pre-RA group were presented before the onset of the disease. While significant differences were found in terms of ST between groups, these differences were not found in terms of SA.	Low
Spector TD	RA	Single-centre retrospective study	657 patients (195 pre-RA; 223 OA; 229 HCs)/1840 pregnancies (519 RA; 679 OA; 642 HCs)	Pre-RA *vs* OA *vs* HC LB: 88% *vs* 80% *vs* 85%; SA: 14.3% *vs* 27.5% *vs* 19.2%; ST: 4.6% *vs* 4.3% *vs* 3%; induced abortions: 6.7% *vs* 5.1% *vs* 6.1%	Women with RA do not have a statistically significant increased rate of SAs or STs before the onset of the disease; having a SA may have a potential 'protective effect' on the development of RA.	Low
Symmons DP	RA	Multicentre retrospective study	230 patients (115 pre-RA; 115 HCs)/No. of pregnancies NF	Pre-RA *vs* HC Parity: 80% *vs* 77%; miscarriages: 24% *vs* 19%	No significant association between groups in terms of APOs.	Low

(continued)

Table 3 Continued

First author	Suspected autoimmune disease	Study design	No. of patients (pre-ARD/ARD/controls)/pregnancies	Pregnancy outcomes (pre-ARD/ARD/control pregnancies)	Summary of findings	Grade of evidence
Van dunne F	RA	Single-centre retrospective study	110 patients (106 pre-RA + 4 RA)/No. of pregnancies NF	Rate of miscarriage: pre-RA+RA: 15%; general population: 12–15%	Miscarriage rates before disease onset in patients with RA are comparable with those reported in the general population, but after the disease has developed, a history of miscarriage may lead to a greater rate of joint destruction.	Low
Alvarez-Nemegyei J	RA	Single-centre retrospective study	47 patients (pre-RA: 29; RA: 36)/120 pregnancies (pre-RA: 61; RA: 59)	Pre-RA *vs* RA Rate of Pec: 1.7% *vs* 11.5% (P =0.12); miscarriages: 18% *vs* 12% (P =0.54)	Compared with pre-RA obstetric events, a higher frequency and number of adverse outcomes was found in pregnancies that occurred after RA onset.	Low
Nelson JL	RA	Multicentre prospective study	749 patients (144 pre-RA; 605 HCs)/2375 pregnancies (455 pre-RA; 1920 HCs)	Pre-RA *vs* HCs SA: 23% *vs* 23%; ST: 3% *vs* 3%; ectopic pregnancy: 3% *vs* 2%	No evidence for difference in pregnancy outcome in patients who subsequently developed RA.	Moderate
Camacho EM	IPA	Multicentre prospective study	1589 IPA patients/1589 pregnancies	25%: 1 APO; 8%: 2 APO; 3%: 3 APO (before the onset). Rate of ST: 14.5/1000; rate of SA: 12.6/100 (similar to UK population)	Similar rates of STs and SAs to that of the general population. Gravid women with a history of 2 or more APOs prior to IPA onset have a worse prognosis in terms of disease than those with 1 or no APOs.	Moderate
Kaplan D	RA	Single-centre prospective study	210 patients (96 pre-RA; 113 HCs)/798 pregnancies (pre-RA: 366; HCs: 432)	Pre-RA *vs* HCs SA: 25% *vs* 16%; LB: 74% *vs* 79%	The risk of SA in the pre-RA group was significantly higher than in the HC group.	Low

Pre-RA: RA before the onset; IPA: inflammatory polyarthritis; AD: autoimmune disease; HC: healthy control; APO: adverse pregnancy outcome; LB: live birth; PB: preterm birth; SA: spontaneous abortion; ST: stillbirth; PL: pregnancy loss (SA+ST); Pec: pre-eclampsia; IUGR: intrauterine growth restriction; AP: abruptio placentae; LBW: low birth weight; ELBW: extreme low birth weight; RR: relative risk; NF: not found; OA: osteoarthritis.

Table 4 Data from original studies of pregnancy outcomes in patients with other pre-ARDs

First author	Suspected autoimmune disease	Study design	No. of patients (pre-ARD/ARD/controls)/pregnancies	Pregnancy outcomes (pre-ARD/ARD/control pregnancies)	Summary of findings	Grade of evidence
Kither H	SLE, APS, CTD	Multicentre retrospective study	117 446 patients (61 pre-SLE; 422 other ARD; 59 pre-APS; 116 904 HCs)/117 446 pregnancies (20 123 with a previous APO; 97 323 HCs)	20123 patients with a previous APO were matched with 97 323 patients with uncomplicated pregnancies. Women with a previous APO had increased risk of developing an ARD or autoimmune antibodies (RR 3.20). This risk was greatest following a ST (RR 5.82) but it was also higher for miscarriage (RR 3.41), Pec/Ec (RR 2.05); PB (RR 2.35); AP (RR 3.39) and IUGR (RR 2.69). Conversely, livebirth was protective against the diagnosis of ARD or APS (RR 0.31)	APO is associated with a significant greater risk of subsequent development of an autoimmune disease. A history of stillbirth has been strongly related, with subsequent diagnosis of both SLE and APS.	Low
Wallenius M	RA/PsA/AS/JIA	Multicentre retrospective study	393 patients (RA+PsA+AS+JIA)/1000 548 pregnancies [548 (pre-ARD including pre-RA+pre-PsA+pre-AS+pre-JIA); 1 000 000: HCs]	Pre-ARD (first birth) *vs* HCs Pec: 4.9% *vs* 4.7%; SGA: 12.6% *vs* 12.1%; perinatal mortality: 0.7% *vs* 0.9%; PB: 7% *vs* 6.3% Pre-ARD (subsequent births) *vs* HCs Pec: 3.8% *vs* 2.1%; SGA: 5.3% *vs* 7.5%; perinatal mortality: 1.1% *vs* 0.8%; PB: 4.6% *vs* 4.9%	APO before the diagnosis (pre-ARD) did not differ from HCs, with the exception of a higher risk of Pec after adjustment for maternal age at delivery. Excess risks of APOs in women diagnosed as having chronic inflammatory arthritides, including a higher rate of perinatal mortality compared with HCs.	Low
Dissanayake TD	RA/PsA	Multicentre retrospective study	103 (RA +PsA)/234 pregnancies (164 pre-disease/70 post-disease)	Pre-RA/PsA *vs* Post-RA/PsA LBW: 4.8% *vs* 7%; birth defects: 6.3% *vs* 5.5%; neonatal medical complications: 15.1% *vs* 21.8%; neonatal ICU complications: 3.2% *vs* 14.5%	A statistically increased neonatal ICU admission rate in pregnancies occurring after the diagnosis of RA/PsA. However, no statistically significant results were found in terms of low birth weight, neonatal medical complications or birth defects when the pre- and post-RA/PsA groups were compared.	Low

(continued)

Table 4 Continued

First author	Suspected autoimmune disease	Study design	No. of patients (pre-ARD/ARD/controls)/pregnancies	Pregnancy outcomes (pre-ARD/ARD/control pregnancies)	Summary of findings	Grade of evidence
Jorgensen KT	RA, SLE, SS	Multicentre retrospective study	1 564 567 patients (51 732 with a subsequent ARD; 1 512 835 HCs)/No. of pregnancies NF	RR of develop an ARD in women with a previous APO *vs* women without gestational complications Hyperemesis (RR = 1.41; 95% CI 1.30, 1.51), gestational hypertensive disorders (1.21; 1.16, 1.26), SA (1.10; 1.07, 1.14) and ST (1.25; 1.12, 1.40).	Overall, compared with women without the specific pregnancy experiences, the risk of any ARD (including RA, SLE, SS and another 28 autoimmune diseases) was significantly increased for women with hyperemesis, gestational hypertensive disorders, SAs or ST.	Low
Siamopoulou-Mavridou A	RA/SLE/SS/SSc/MCTD	Single-centre retrospective study	252 patients [(40 SLE; 72 RA; 21 SS; 14 SSc; 7 MCTD; 98 HCs)]/686 pregnancies (pre-SLE: 81; SLE: 14; pre-RA: 191; RA: 15; pre-SS: 63; pre-SSc: 36; MCTD: 19; HCs: 267)	Pre-SLE *vs* SLE *vs* pre-RA *vs* RA *vs* pre-SS *vs* pre-SSc *vs* MCTD *vs* HCs LB: 85% *vs* 79% *vs* 81% *vs* 73% *vs* 76% *vs* 78% *vs* 84% *vs* 85%; PB: 5% *vs* 7% *vs* 1% *vs* 0% *vs* 0% *vs* 0% *vs* 0% *vs* 1%; SA: 9% *vs* 0% *vs* 16% *vs* 27% *vs* 21% *vs* 22% *vs* 16% *vs* 12%; ST: 1% *vs* 14% *vs* 2% *vs* 0% *vs* 3% *vs* 0% *vs* 0% *vs* 3%; FL (SA+ST): 10% *vs* 14% *vs* 18% *vs* 27% *vs* 24% *vs* 22% *vs* 16% *vs* 15%	Subclinical factors in patients with ARD before their disease onset, do not appear to influence significantly the outcomes of pregnancies of these individuals.	Low
McHugh NJ	RA/SLE	Single-centre prospective study	319 patients (117 RA; 74 SLE, 28 SSc, 100 HCs)/816 pregnancies (292 RA; 131 SLE; 81 SSc; 312 HCs)	Pre-RA *vs* pre-SLE *vs* pre-SSc *vs* HCs SA: 15% *vs* 10% *vs* 33% *vs* 16%	Women destined to develop SSc, in contrast to SLE and RA, have an increased risk of SA compared with HC.	Low
Van Wyk L	SSc	Dual-centre retrospective study	206 patients (103 pre-SSc; 103 HCs)/502 pregnancies (254 pre-SSc; 248 HCs)	Pre-SSc *vs* HCs Hypertensive disorders: 26% *vs* 13%; IUGR: 13% *vs* 4%; miscarriages: 32% *vs* 1%	Women who later developed SSc, there was an increased incidence of pregnancy complications, such as hypertension, IUGR or miscarriages; compared with controls.	Low

Pre-SLE: SLE before the onset; pre-APS: APS before the onset; pre-RA: RA before the onset; HC: healthy control; APO: adverse pregnancy outcome; PB: preterm birth; SA: spontaneous abortion; ST: stillbirth; SGA: small-for-gestational-age; Pec: pre-eclampsia; Ec: eclampsia; IUGR: intrauterine growth restriction; AP: abruptio placentae; LBW: low birth weight; ICU: intensive care unit; RR: relative risk; MCTD: Mixed Connective Tissue Disease; NF: not found.

increased risk has been firmly established in SLE by several large (mostly retrospective) population-based studies and a 2016 meta-analysis demonstrating an increased risk of a range of maternal and foetal APOs, such as gestational hypertension, pre-eclampsia, pre-term labour, intrauterine growth restriction (IUGR) and small-for-gestational-age [1, 35, 36]. In RA pregnancies, there are conflicting reports of the occurrence of APOs. Overall, most studies found women with RA to have a significantly increased risk of gestational hypertension, pre-eclampsia, IUGR, premature delivery, and caesarean delivery, and an increased length of hospital stay, although not all studies found a significant association with hypertensive disorders of pregnancy [1]. In SLE and RA pregnancies, however, there are clear links between increased disease activity immediately prior to and during pregnancy and subsequent APOs [37].

It is less clear, however, whether an increased risk of APOs exists in women before they are diagnosed with an ARD many years post-partum. Classification criteria developed to identify a homogeneous group of patients with a specific ARD for inclusion in research studies are widely used in clinical practice to aid diagnosis and management [38–39]. Not all patients, however, fulfil the relevant classification criteria, and while they cannot then be included in research studies they can be described as having either incomplete or non-criteria forms of the disease and treated accordingly [40–41]. It has been shown that up to 50% of patients with incomplete forms of lupus progress to SLE [42], and ∼20% of patients with clinically suspect arthralgia progress to RA [43]. Therefore, not all patients with incomplete ARDs will progress to complete forms of disease. In contrast, the concept of a pre-ARD has been used to refer to patients who later in life developed an ARD. It is most recognized in RA, where the transition from health to established disease is relatively well understood, such that EULAR recommendations including terminology relating to pre-RA [44] and a set of clinical characteristics describing arthralgia at risk of RA [45] have been established. Studies leveraging the large, longitudinal Department of Defence Serum Repository have shown that, for many patients, SLE classification is preceded by a period of autoantibody positivity and other immune dysregulation, even in the absence of clinical symptoms [46, 47]. For the purpose of this review, we defined preclinical disease as subsequent diagnosis with a complete form of ARD. Fourteen articles examined APO in pre-SLE ($n > 1000$ pre-SLE pregnancies), GenPop pregnant women and/or SLE patients [3–5, 8, 9, 14–22]. Overall, the reported findings demonstrate an increased risk of APOs in pre-SLE pregnancies and support the idea that a preclinical state of SLE disease negatively affects pregnancy outcomes. In line with this result, a series of studies by Spinillo *et al.* reported that women with an unrecognized ARD before conception had an increased risk of developing APOs compared with healthy pregnant women [48–50]. None of the 14 studies identified proposed any specific intervention related to preclinical disease other than appropriate management of APOs. APOs such as pre-eclampsia, IUGR or preterm birth, can be an early manifestation of an ARD, and therefore they may alert clinicians. A review by Spinillo *et al.* [51] also reported the importance of being aware that ARDs in their early/undifferentiated stages can affect pregnancy by increasing the chances of developing APOs. Our results underline the importance of questioning patients about their past obstetric history when evaluating possible development of subsequent ARDs. In addition, the development of novel screening strategies and/or discovery of new biomarkers to recognize those patients before onset of the ARD might reduce APOs. A recent study from Nalli *et al.* [52] found that decreased complement levels before pregnancy were associated with an increased risk of APOs in patients with APS who were triple (aCL, anti-ß2Glycoprotein I and LA) positive and asymptomatic triple-positive aPL carriers. Complement levels are cheap and easily measured and are known to be involved in the physiopathology of ARDs [53, 54]. Therefore, measurement of complement in addition to other biomarkers associated with APOs (e.g. aPL and anti-Ro/La antibodies) may prove useful in patients with initial symptoms of ARDs to identify patients at increased risk of APOs.

The second group of publications we found examined pre-RA pregnancy outcomes ($n > 1600$ pre-RA pregnancies). Of 15 studies [6, 7, 9–11, 18, 19, 23–30] examining pregnancy outcomes in women with pre-RA, GenPop pregnant women and/or RA patients, most did not find any differences in pregnancy outcomes between patients who subsequently developed RA and healthy controls (HCs).

The third group of publications ($n > 900$ pre-ARD pregnancies) examined pregnancy outcomes in a wide variety of pre-ARDs (eg: pre-SSc, pre-SS, pre-PsA). Less data exists on pregnancy outcomes in these populations compared with RA and SLE, and it is even more limited when comparing them with pregnancy outcomes in their pre-ARD states. We found only seven articles examining the impact of other pre-ARDs on pregnancy outcomes. Therefore, it is difficult to draw conclusions, given the small numbers of patients, the low quality of the evidence, and the disparate immunopathology of ARDs included in this section.

Jorgensen *et al.* [18] proposed that abnormal pregnancies are associated with increased risk of certain ARDs, possibly because of underlying immunologic or hormonal factors that predispose to both APOs and ARD development. Spontaneous losses may have a different pathogenesis than other APOs, such as IUGR, stillbirth or pre-eclampsia. While spontaneous loss complications are mainly related to genetic abnormalities, or endocrine or anatomical factors [55], the other named APOs may be caused by vascular placental insufficiency [56]. Spontaneous losses are also frequently underestimated, due to underreporting, so information on their frequency should be cautiously interpreted.

The precise mechanisms of APOs remain unknown. It is likely that the pathogenic mechanisms of APOs in

pre-ARDs will be similar to those identified in ARDs, including defects in various immunoregulatory pathways leading to activation of inflammatory mediators, and endothelial damage at the materno–foetal interface causing placental insufficiency [56, 57]. Therefore, abnormalities present during preclinical disease, such as the development of asymptomatic autoimmunity and elaboration of an immune or inflammatory response [2], may be responsible for APOs in the pre-disease state. We found the greatest risk of APOs in pre-SLE pregnancies compared with other pre-ARDs. Ullf-Moller [16] hypothesized that poor foetal outcomes might be indicative of a pre-disease state in which subclinical SLE complicates pregnancies before the disease itself becomes clinically apparent. Kither *et al.* [17] proposed that either immunological factors may predispose women to APOs and subsequent ARD diagnosis or that APOs initiate autoimmune events that culminate in ARDs in later life. Ultimately, further research is required to elucidate the precise mechanisms and determine whether any specific intervention is required.

Limitations of the literature

Our findings are limited by the high heterogeneity in the methodology of the various studies we identified, such as: the small number of patients and pregnancies in some studies; the differences in the included pregnancies (multiple pregnancies or singletons); the lack of disease activity data in those with confirmed/complete disease; the use of self-reported surveys of previous APOs, where quality would be downgraded due to selection and recall bias; the scarcity of data on timing of pregnancy and ARD onset; and the lack of either a healthy pregnancy and/or ARD control group.

We have tried to consider how these limitations may have impacted our findings. Regarding the sample size, it is known that confounding may occur with small sample size; however, wherever you draw a cut-off for sample size, the result remains the same, since nearly all (10/11 studies in pre-SLE *vs* GenPop pregnancies; 7/10 studies in pre-SLE *vs* SLE studies and 10/13 studies in pre-RA *vs* GenPop pregnancies) found the same result. Considering only studies with $\geq$200 (pre-ARD + ARD) pregancies, we found that: 6/7 studies [3, 4, 14, 16–19] reported that pre-SLE patients have increased APOs compared with the GenPop; 2/3 studies [3, 4, 14] reported that SLE patients experienced more APOs than pre-SLE pregnancies. In addition, 5/6 of the RA studies [18, 19, 23, 26, 27, 30] found that pre-RA patients have similar pregnancy outcomes to the GenPop. Therefore, the results of this secondary analysis are in line with our previous conclusions in the manuscript, and sample size does not appear to have been an important bias for our systematic review.

It is hard to determine the precise impact of the other limitations, due to the small number of papers that addressed each one, and their findings were similar to the majority of other papers with these potential limitations. For instance, inclusion of single/multiple pregnancies may adversely affect comparison of outcomes, such as birthweight, that increase with subsequent pregnancies, yet only 1/21 studies [14] clearly stated whether pregnancies were single/multiple. The lack of disease activity data is important, since active disease is known to be associated with APOs, and only 4/15 studies [21, 25, 26, 28] with an ARD control group evaluated disease activity in those patients. Self-reported surveys of previous APOs may be prone to recall bias or error, and 8/21 of the studies [7, 11, 23–26, 28, 29] performed a survey to extract personal information about patients who were no different from remaining studies of clinician-reported outcomes. The timing of pregnancy in relation to onset of the ARD is important, since disease onset within 6 months of an APO may have a different pathogenesis compared with disease that develops several years after the APO, and only 2/21 studies [14, 15] described this data. Although a lack of healthy and/or ARD pregnancy control groups would hamper interpretation of findings in pre-ARD pregnancies, 25/27 of the studies were compared with ARD pregnancies and/or GenPop pregnancies. Therefore, we believe that this limitation did not have a great impact on our results.

In addition, the retrospective nature of many of the studies often meant there was missing data, such as incomplete information on the various possible complications during pregnancy, or lack of information on treatments used and/or other comorbidities, which limited our ability to identify associations with APO. Therefore, the overall quality of the evidence was low, which limits the strength of our conclusions.

In terms of the pre-RA studies, another limitation we found was the limited information about positivity for relevant antibodies such as RF or anti-CCP in the pre-RA pregnancy outcomes.

Furthermore, potential publication bias could affect the strength of any systematic review, as some papers with null results to this hypothesis were possibly not published.

Conclusion

Overall, published studies found that patients with SLE have the highest risk of APOs, while pre-SLE pregnancies also have an increased burden of APOs when compared with GenPop pregnant women. In contrast, a similar rate of APOs was reported when pre-RA and healthy pregnancies were compared. Pre-SSc was associated with an increased risk of spontaneous abortion, but a similar risk of obstetric complications to that of the GenPop was found in the included studies when other pre-ARDs were examined. These findings highlight the importance of taking an obstetric history at the first review in a rheumatology clinic, the need for novel screening strategies for the prediction of APOs, and for further research to elucidate the immune basis of APOs in preclinical and clinical ARD.

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Data availability statement

The original contributions presented in the study are included in the article/supplementary files. Further inquiries can be directed to the corresponding author or second author.

References

1 Giles I, Yee CS, Gordon C. Stratifying management of rheumatic disease for pregnancy and breastfeeding. Nat Rev Rheumatol 2019;15:391–402.

2 Raza K, Gerlag DM. Preclinical inflammatory rheumatic diseases: an overview and relevant nomenclature. Rheum Dis Clin North Am 2014;40:569–80.

3 Barnado A, Wheless L, Meyer AK, Gilkeson GS, Kamen DL. Pregnancy outcomes among African-American patients with systemic lupus erythematosus compared with controls. Lupus Sci Med 2014;1:e000020.

4 Petri M, Allbritton J. Fetal outcome of lupus pregnancy: a retrospective case–control study of the Hopkins Lupus Cohort. J Rheumatol 1993;20:650–6.

5 Hardy CJ, Palmer BP, Morton SJ, Muir KR, Powell RJ. Pregnancy outcome and family size in systemic lupus erythematosus: a case–control study. Rheumatology (Oxford) 1999;38:559–63.

6 Kaplan D. Fetal wastage in patients with rheumatoid arthritis. J Rheumatol 1986;13:875–7.

7 Silman AJ, Roman E, Beral V, Brown A. Adverse reproductive outcomes in women who subsequently develop rheumatoid arthritis. Ann Rheum Dis 1988;47:979–81.

8 Julkunen H, Jouhikainen T, Kaaja R *et al.* Fetal outcome in lupus pregnancy: a retrospective case–control study of 242 pregnancies in 112 patients. Lupus 1993;2:125–31.

9 Siamopoulou-Mavridou A, Manoussakis MN, Mavridis AK, Moutsopoulos HM. Outcome of pregnancy in patients with autoimmune rheumatic disease before the disease onset. Ann Rheum Dis 1988;47:982–7.

10 Nelson JL, Voigt LF, Koepsell TD, Dugowson CE, Daling JR. Pregnancy outcome in women with rheumatoid arthritis before disease onset. J Rheumatol 1992;19:18–21.

11 Symmons DP, Bankhead CR, Harrison BJ *et al.* Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care–based incident case–control study in Norfolk, England. Arthritis Rheum 1997;40:1955–61.

12 Liberati A, Altman DG, Tetzlaff J *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.

13 Arkema EV, Palmsten K, Sjöwall C *et al.* What to expect when expecting with systemic lupus erythematosus (SLE): a population-based study of maternal and fetal outcomes in SLE and pre-SLE. Arthritis Care Res (Hoboken) 2016;68:988–94.

14 Guyatt GH, Oxman AD, Vist GE *et al.*; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.

15 Dhar JP, Essenmacher LM, Ager JW, Sokol RJ. Pregnancy outcomes before and after a diagnosis of systemic lupus erythematosus. Am J Obstet Gynecol 2005;193:1444–55.

16 Ulff-Møller CJ, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Reproductive factors and risk of systemic lupus erythematosus: nationwide cohort study in Denmark. J Rheumatol 2009;36:1903–9.

17 Kither H, Heazell A, Bruce IN, Tower C, Crocker I. Adverse pregnancy outcomes and subsequent development of connective tissue disease in the UK: an epidemiological study. BJOG 2020;127:941–9.

18 Jørgensen KT, Nielsen NM, Pedersen BV, Jacobsen S, Frisch M. Hyperemesis, gestational hypertensive disorders, pregnancy losses and risk of autoimmune diseases in a Danish population-based cohort. J Autoimmun 2012;38:J120–8.

19 McHugh NJ, Reilly PA, McHugh LA. Pregnancy outcome and autoantibodies in connective tissue disease. J Rheumatol 1989;16:42–6.

20 Johns KR, Morand EF, Littlejohn GO. Pregnancy outcome in systemic lupus erythematosus (SLE): a review of 54 cases. Aust N Z J Med 1998;28:18–22.

21 Kiss E, Bhattoa HP, Bettembuk P, Balogh A, Szegedi G. Pregnancy in women with systemic lupus erythematosus. Eur J Obstet Gynecol Reprod Biol 2002;101:129–34.

22 Kleinman D, Katz VL, Kuller JA. Perinatal outcomes in women with systemic lupus erythematosus. J Perinatol 1998;18:178–82.

23 Kay A, Bach F. Subfertility before and after the development of rheumatoid arthritis in women. Ann Rheum Dis 1965;24:169–73.

24 Spector TD, Silman AJ. Is poor pregnancy outcome a risk factor in rheumatoid arthritis? Ann Rheum Dis 1990;49:12–4.

25 Van Dunné FM, Lard LR, Rook D, Helmerhorst FM, Huizinga TW. Miscarriage but not fecundity is associated with progression of joint destruction in rheumatoid arthritis. Ann Rheum Dis 2004;63:956–60.

26 Camacho EM, Verstappen SM, Lunt M, Bunn DK, Symmons DP. Multiple adverse pregnancy outcomes before symptom onset are associated with a worse

disease outcome in women with recent-onset inflammatory polyarthritis. Ann Rheum Dis 2012;71:528–33.

27 Ma KK, Nelson JL, Guthrie KA, Dugowson CE, Gammill HS. Adverse pregnancy outcomes and risk of subsequent rheumatoid arthritis. Arthritis Rheumatol 2014;66:508–12.

28 Dissanayake TD, Maksymowych WP, Keeling SO. Peripartum issues in the inflammatory arthritis patient: a survey of the RAPPORT registry. Sci Rep 2020;10:3733.

29 Alvarez-Nemegyei J, Cervantes-Díaz MT, Avila-Zapata F, Marín-Ordóñez J. Desenlace obstétrico antes y después del inicio de la artritis reumatoide [Pregnancy outcomes before and after the onset of rheumatoid arthritis]. Rev Med Inst Mex Seguro Soc 2011;49:599–604.

30 Wallenius M, Skomsvoll JF, Irgens LM *et al.* Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. Arthritis Rheum 2011;63:1534–42.

31 Van Wyk L, Van der Marel J, Schuerwegh AJ *et al.* Increased incidence of pregnancy complications in women who later develop scleroderma: a case control study. Arthritis Res Ther 2011;13:R183.

32 Nalli C, Iodice A, Andreoli L *et al.* The effects of lupus and antiphospholipid antibody syndrome on foetal outcomes. Lupus 2014;23:507–17.

33 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.

34 Chakravarty EF, Nelson L, Krishnan E. Obstetric hospitalizations in the United States for women with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum 2006;54:899–907.

35 Bundhun PK, Soogund MZ, Huang F. Impact of systemic lupus erythematosus on maternal and fetal outcomes following pregnancy: a meta-analysis of studies published between years 2001–2016. J Autoimmun 2017;79:17–27.

36 Chen CY, Chen YH, Lin HC, Chen SF, Lin HC. Increased risk of adverse pregnancy outcomes for hospitalisation of women with lupus during pregnancy: a nationwide population-based study. Clin Exp Rheumatol 2010;28:49–55.

37 De Man YA, Hazes JM, van der Heide H *et al.* Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. Arthritis Rheum 2009;60:3196–206.

38 Miyakis S, Lockshin MD, Atsumi T *et al.* International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.

39 Petri M, Orbai AM, Alarcón GS *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.

40 Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R et al; for the EUROAPS Study Group. Comparative study of obstetric antiphospholipid syndrome (OAPS) and non-criteria obstetric APS (NC-OAPS): report of 1640 cases from the EUROAPS registry. Rheumatology (Oxford) 2020;59:1306–14.

41 Arachchillage DR, Machin SJ, Mackie IJ, Cohen H. Diagnosis and management of non-criteria obstetric antiphospholipid syndrome. Thromb Haemost 2015;113:13–9.

42 Rúa-Figueroa Í, Richi P, López-Longo FJ *et al.*; EAS-SER (Systemic Diseases Study Group of the Spanish Society of Rheumatology). Comprehensive description of clinical characteristics of a large systemic lupus erythematosus cohort from the Spanish Rheumatology Society Lupus Registry (RELESSER) with emphasis on complete versus incomplete lupus differences. Medicine (Baltimore) 2015;94:e267.

43 van Steenbergen HW, Mangnus L, Reijnierse M, Huizinga TWJ, van der Helm-van Mil AHM. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. Ann Rheum Dis 2016;75:1824–30.

44 Gerlag DM, Raza K, van Baarsen LGM *et al.* EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. Ann Rheum Dis 2012;71:638–41.

45 Van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ *et al.* EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Ann Rheum Dis 2017;76:491–6.

46 Arbuckle MR, McClain MT, Rubertone MV *et al.* Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1526–33.

47 Heinlen LD, McClain MT, Merrill J *et al.* Clinical criteria for systemic lupus erythematosus precede diagnosis, and associated autoantibodies are present before clinical symptoms. Arthritis Rheum 2007;56:2344–51.

48 Spinillo A, Beneventi F, Locatelli E *et al.* The impact of unrecognized autoimmune rheumatic diseases on the incidence of preeclampsia and fetal growth restriction: a longitudinal cohort study. BMC Pregnancy Childbirth 2016;16:313.

49 Spinillo A, Beneventi F, Locatelli E *et al.* Early, incomplete, or preclinical autoimmune systemic rheumatic diseases and pregnancy outcome. Arthritis Rheumatol 2016;68:2555–62.

50 Spinillo A, Beneventi F, Ramoni V *et al.* Prevalence and significance of previously undiagnosed rheumatic diseases in pregnancy. Ann Rheum Dis 2012;71:918–23.

51 Spinillo A, Beneventi F, Caporali R, Ramoni V, Montecucco C. Undifferentiated connective tissue diseases and adverse pregnancy outcomes. An undervalued association? Am J Reprod Immunol 2017;78:e12762.

52 Nalli C, Lini D, Andreoli L *et al.* Low preconception complement levels are associated with adverse pregnancy outcomes in a multicenter study of 260 pregnancies in 197 women with antiphospholipid syndrome or carriers of antiphospholipid antibodies. Biomedicines 2021;9:671.

53 Chighizola CB, Lonati PA, Trespidi L, Meroni PL, Tedesco F. The complement system in the pathophysiology of pregnancy and in systemic autoimmune rheumatic diseases during pregnancy. Front Immunol 2020;11:2084.

54 Dijkstra DJ, Joeloemsingh JV, Bajema IM, Trouw LA. Complement activation and regulation in rheumatic disease. Semin Immunol 2019;45:101339.

55 Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. Rev Obstet Gynecol 2009;2:76–83.

56 Østensen M, Andreoli L, Brucato A *et al.* State of the art: reproduction and pregnancy in rheumatic diseases. Autoimmun Rev 2015;14:376–86.

57 Østensen M, Cetin I. Autoimmune connective tissue diseases. Best Pract Res Clin Obstet Gynaecol 2015;29: 658–70.