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ORIGINAL RESEARCH

Management of pregnancy in autoimmune rheumatic diseases: maternal disease course, gestational and neonatal outcomes and use of medications in the prospective Italian P-RHEUM.it study

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Reproductive health and pregnancy are of fundamental importance for women living with autoimmune rheumatic diseases (ARD). Prospectively collected data from large cohorts about the impact of current rheumatology practice (disease remission strategies and use of targeted treatments) on pregnancy outcomes is still limited.

WHAT THIS STUDY ADDS

⇒ Our study captured the Italian real-world experience in managing pregnancies in patients with ARD in 2018–2023. Pregnancy planning, use of compatible medications, stable disease control and tight multispecialistic monitoring were probably the key elements contributing to a low frequency of disease flares and to pregnancy outcomes similar to those reported in the general obstetric population, including a high proportion of live births.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings can aid healthcare professionals in preconception counselling and reassure women with ARD that risk stratification and individualised treatment approach offered by a multidisciplinary team can minimise disease-related risks, yielding successful maternal and neonatal outcomes in most cases.

ABSTRACT

Objectives To investigate pregnancy outcomes in women with autoimmune rheumatic diseases (ARD) in the Italian prospective cohort study P-RHEUM.it.

Methods Pregnant women with different ARD were enrolled for up to 20 gestational weeks in 29 Rheumatology Centres for 5 years (2018–2023). Maternal and infant information were collected in a web-based database.

Results We analysed 866 pregnancies in 851 patients (systemic lupus erythematosus was the most represented disease, 19.6%). Maternal disease flares were observed in 135 (15.6%) pregnancies. 53 (6.1%) pregnancies were induced by assisted reproduction techniques, 61 (7%) ended in miscarriage and 11 (1.3%) underwent elective termination. Obstetrical complications occurred in 261 (30.1%) pregnancies, including 2.3% pre-eclampsia. Two cases of congenital heart block were observed out of 157 pregnancies (1.3%) with anti-Ro/SSA. Regarding treatments, 244 (28.2%) pregnancies were treated with glucocorticoids, 388 (44.8%) with hydroxychloroquine, 85 (9.8%) with conventional synthetic disease-modifying anti-rheumatic drugs and 122 (14.1%) with biological disease-modifying anti-rheumatic drugs. Live births were 794 (91.7%), mostly at term (84.9%); four perinatal deaths (0.5%) occurred. Among 790 newborns, 31 (3.9%) were small-for-gestational-age and 169 (21.4%) had perinatal complications. Exclusive maternal breast feeding was received by 404 (46.7%) neonates. The Edinburgh Postnatal Depression Scale was compiled by 414 women (52.4%); 89 (21.5%) scored positive for emotional distress.

Conclusions Multiple factors including preconception counselling and treat-to-target with pregnancy-compatible medications may have contributed to mitigate disease-related risk factors, yielding limited disease flares, good pregnancy outcomes and frequency of complications which were similar to the Italian general obstetric population. Disease-specific issues need to be further addressed to plan preventative measures.

INTRODUCTION

Autoimmune rheumatic diseases (ARD) frequently affect female individuals of childbearing age; therefore, reproductive issues are of fundamental importance in the management of women living with these chronic diseases. Treatment strategies for ARD have significantly improved over the last few decades, facilitating permissive conditions for a pregnancy,[1 2] but also posing new challenges such as the use of novel antirheumatic drugs in pregnancy and lactation.[3] Adequate knowledge about the implications of ARD on reproductive health is essential for physician–patient communication, hence scientific societies produced recommendations and guidelines to assist healthcare professionals.[4–8] However, these sets of guidance were mostly based on low-quality evidence and expert opinion, due to the paucity of randomised controlled trials and prospective studies of adequate sample size involving pregnant patients with ARD.

The need for evidence-based answers to the most common questions of women with ARD who are planning a pregnancy[9] prompted researchers to set up prospective cohorts of pregnant patients and national Pregnancy Registries in several Countries worldwide.[3 10] In order to facilitate harmonisation and standardisation in collected variables, a EULAR Task Force was convened to define a core data set for registries and observational studies that prospectively collect information about pregnant women with ARD and their infants.[11]

In 2017, the Italian Society for Rheumatology (SIR) promoted a prospective cohort study called P-RHEUM.it (The ITalian registry of Pregnancy in the RHEUMatic diseases). Its purpose was to address several primary and secondary objectives regarding maternal disease course during pregnancy, pregnancy outcomes and maternal/infant outcomes after delivery, with a focus on patient-reported outcomes (PROs) by means of validated questionnaires.

We report an ad-interim descriptive analysis to provide a general overview of the real-world experience of pregnancy in ARD regarding maternal disease flares, adverse pregnancy outcomes (APO), neonatal complications and use of medications according to the current standard of care in rheumatology.

PATIENTS AND METHODS

Study design

The P-RHEUM.it study is a multicentre, nationwide, hospital-based, observational prospective cohort study. Pregnant women with ARD were enrolled in 29 rheumatology centres affiliated with SIR and followed-up in a multidisciplinary fashion, either in collaboration with local Obstetricians-Gynaecologists (Ob/Gyn) or within a joint pregnancy clinic with Ob/Gyn who are dedicated to high-risk pregnancies (in 13 centres). The enrolment spanned over 5 years from 4 May 2018 to 3 May 2023.

The study design included six time points during and after pregnancy (online supplemental figure 1): a baseline visit, one visit during each trimester, a visit at 30–60 days after delivery and a visit at 6 months after delivery. Maternal variables included socio-demographic

features, disease characteristics, obstetric history and disease flares/obstetrical complications during the index pregnancy. Pregnancy outcomes and neonatal conditions were also captured. At each time point during pregnancy, patients were asked to compile questionnaires regarding the quality of life (QoL) and the assessment of their health by means of EuroQoL instrument EQ-5D-3L (−1.6: poorest QoL; 1: excellent QoL)[12] and Patient Global Health - Visual Analogic Scale (0–100; 0 poorest health – 100 full health),[13] respectively. During each of the two visits after delivery, the Edinburgh Postnatal Depression Scale (EPDS)[14 15] was administered to the patients; the same questionnaire was also proposed via a web-link at 12 months after delivery. A questionnaire regarding the health conditions of the infant was administered to the mother at the 6 months post-delivery visit and via an electronic web-link at 12 and 24 months of age.

At each visit, the medical investigator was asked to provide a Physician's Global Assessment (PGA) score ranging 0–100 (0: no activity; 100: highest activity), reflecting the physician's judgement of the need to increase or reduce therapy based on disease activity. Due to the lack of validation of disease activity instruments during pregnancy in most ARD,[16] we chose an operational definition of flare based on the need to increase the dosage of medications or to start a new therapy.

The study protocol is available as online supplemental material. Patient representatives were not involved in the design of the study. Inclusion and exclusion criteria are reported in table 1.

Table 1 Inclusion and exclusion criteria of the P-RHEUM.it study

Inclusion criteria	
A	Age 18–45 years
B	To be pregnant within the 20th gestational week
C	To be classified as: (1) definite autoimmune rheumatic disease (ARD) according to international classification criteria for each disease, or (2) asymptomatic carriers of antiphospholipid antibodies (aPL) or anti-Ro/SSA antibodies. Included ARD: 1. Rheumatoid arthritis. 2. Psoriatic arthritis. 3. Spondyloarthritis. 4. Juvenile idiopathic arthritis. 5. Undifferentiated arthritis. 6. Systemic lupus erythematosus. 7. Primary antiphospholipid syndrome. 8. Undifferentiated connective tissue disease. 9. Sjögren's syndrome. 10. Systemic sclerosis. 11. Idiopathic inflammatory myopathies. 12. Systemic vasculitis.
Exclusion criteria	
A	Being affected by organ-specific autoimmune disease only (no systemic autoimmune disease).
B	Asymptomatic individuals without a persistent positivity for aPL and/or anti-Ro/SSA (transiently or intermittently positive).
C	Inability to understand the study and give informed consent and/or to regularly attend follow-up visits.

Data collection

Consecutive pregnant patients fulfilling the criteria were asked to participate in the study and enrolled after signed informed consent, also obtained by the father regarding the collection of the infant's data.

Anonymised clinical and laboratory data, general and disease-specific measurements (online supplemental table 1), and answers to questionnaires were collected and managed using Research Electronic Data Capture tools[17 18] hosted at the Epidemiology Research Unit of SIR.

Statistical analysis

The selection of pregnancies to be analysed was performed on all pregnancies potentially ended by at least 90 days from the data extraction date (8 November 2023), on fulfilment of inclusion criteria, singleton status and complete data entry at least up to the visit at 30–60 days after delivery. The estimated date of delivery was calculated based on the first day of the last menstrual period (which could be the actual one or the estimated one based on fetal ultrasound). The flowchart is depicted in figure 1.

Data were descriptively analysed and reported as numbers and percentages for categorical variables and as median values (IQR) for continuous variables. Proportions were calculated according to the appropriate denominator, considering different groups such as patients, pregnancies or neonates. Missing data were reported when appropriate. All data processing was performed using R V.4.2.2 (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Over the study period, 1298 pregnancies were enrolled. We analysed 866 singleton pregnancies in 851 patients with ARD enrolled in 27 centres. The distribution of maternal diseases is shown in figure 2. A diagnosis of inflammatory arthritis (IA) was present in 276 (32.4%) patients, while 557 (65.5%) belonged to the group of connective tissue diseases (CTD) - systemic vasculitis (SV) (including antiphospholipid antibodies (aPL) carriers); 18 (2.1%) women were asymptomatic carriers of anti-Ro/SSA antibodies.

Maternal and disease characteristics

The median age at conception was 34 (IQR 31–37) years; 89% of the patients were Caucasian. Disease duration at enrolment was 6.4 (IQR 2.6–11.4) years. Other features about demography and obstetric history can be found in table 2, while features regarding family status, education level, lifestyle habits, comorbidities and associated

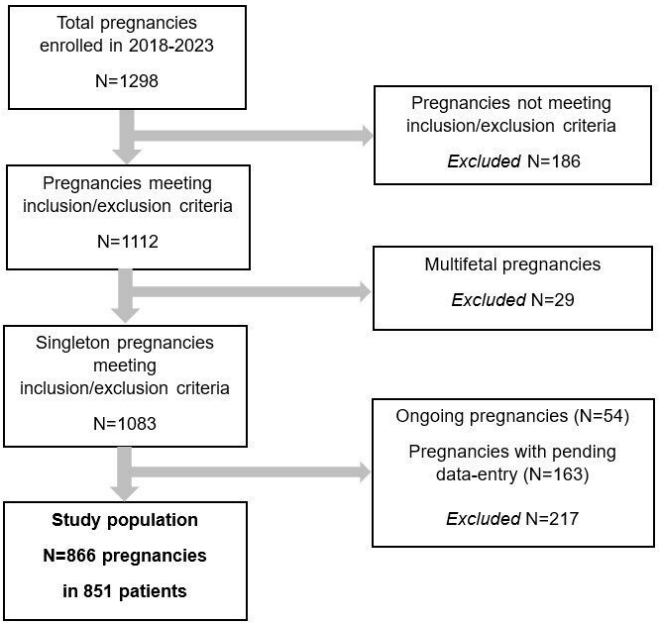

Figure 1 Flowchart showing the selection of pregnancies included in the analysis.

autoimmune diseases can be found in online supplemental table 2. The frequency of positive disease-specific/disease-associated autoantibody/laboratory markers is presented in online supplemental table 3. Flares in the 12 months prior to conception were reported by the medical investigator in 180 (21.2%) patients; PGA at enrolment was 4 (IQR 0–13.5), indicating remission or low disease activity. Most patients reported a good health status both in the 12 months prior to conception and at enrolment, with Patient Global Health values of 95 (IQR 80–100) and 80 (IQR 70–90), respectively. Patients also reported a good QoL at enrolment, with EQ-5L-3D scores of 1 (IQR 0.8–1) (online supplemental table 4).

Pregnancy and neonatal outcomes

Patients were enrolled at a median gestational age of 11 weeks (IQR 8–15); 355 (41.7%) were primigravida. More than one pregnancy in the same woman was registered in 14 cases (1.6%) (figure 3). Maternal disease flares were observed in 135 (15.6%) pregnancies, ranging from 8.8% in undifferentiated connective tissue disease to 26.1% in psoriatic arthritis (PsA) (table 3). No maternal deaths occurred during the study period.

Out of 866 pregnancies (table 3), 61 (7%) ended in miscarriage, and 11 (1.3%) underwent elective termination (1 due to malformation); 53 (6.1%) had been induced by assisted reproduction techniques (ARTs). Obstetrical complications occurred in 261 (30.1%) pregnancies, including 20 (2.3%) pregnancies complicated by pre-eclampsia (PE), 61 (7%) by gestational diabetes and 35 (4%) by gestational hypothyroidism (online supplemental table 5). Fetal growth restriction (FGR) was detected in 69 (8%) of pregnancies, 15 (5.3%) in 281 IA pregnancies, 52 (9.2%) in 567 CTD-SV pregnancies and in 2 pregnancies (11.1%) in anti-Ro/SSA carriers. Congenital heart block (CHB) was diagnosed in two fetuses of patients carrying anti-Ro/SSA antibodies, namely one patient with systemic lupus erythematosus (SLE) and one asymptomatic carrier. In our cohort, the incidence of CHB was 2 cases out of 157 pregnancies (1.3%) in women with anti-Ro/SSA.

Live births were 794 (91.7%); 4 perinatal deaths (0.5%) occurred, all in newborns of patients with SLE (3 cases due to very severe preterm delivery caused by PE; 1 case due to myocarditis associated with CHB). Most neonates were born at term (84.9%); severe preterm birth (PTB) before 34 gestational weeks (GWs) occurred in 26 (3.3%) cases. Vaginal delivery was carried out in 463 (53.5%) cases; caesarean section (C-section) was performed in 312 (39.3%) cases, 61.5% elective and 38.5% emergent.

Among 790 newborns who were alive at 28 days after delivery, 31 (3.9%) were classified as small-for-gestational-age (SGA), 16 (2%) displayed congenital malformations, and 169 (21.4%) suffered from complications at birth (table 4). Exclusive maternal breast feeding was received by 404 (46.7%) neonates in the first month of life. EPDS was compiled by 414women (52.4%) at 1–2

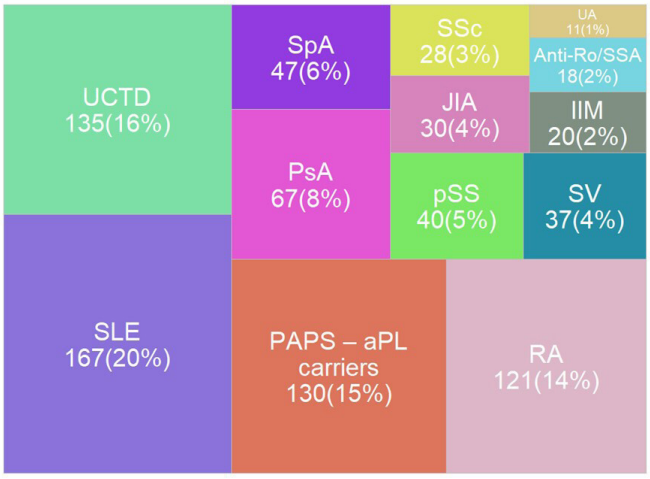

Figure 2 Tree map reporting the number of patients included in the study according to their diagnosis of autoimmune rheumatic disease. Patients with RA, PsA, SpA, JIA, UA were labelled as IA group, while patients with SLE, PAPS/aPL carriers, UCTD, pSS, SSc, IIM as CTD group. The IIM group included 6 patients with polydermatomyositis and 14 with mixed connective tissue disease. The SV group comprised 23 patients with Behçet's disease, 6 with Takayasu arteritis, 5 with ANCA-associated vasculitis and 3 with Cogan's syndrome. anti-Ro/SSA, asymptomatic carriers of anti-Ro/SSA antibodies; CTD, connective tissue diseases; IA, inflammatory arthritis; IIM, idiopathic inflammatory myopathies; JIA, juvenile idiopathic arthritis; PAPS-aPL carriers, primary antiphospholipid syndrome and antiphospholipid antibody (aPL) carriers; PsA, psoriatic arthritis; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SSc, systemic sclerosis; SV, systemic vasculitis; UA, undifferentiated arthritis; UCTD, undifferentiated connective tissue disease.

Table 2 Maternal features regarding demographics and obstetric history. For women with more than one pregnancy enrolled in the study, the information related to the first enrolled pregnancy was considered. Categorical variables are expressed as numbers (percentages) and continuous variables as median (IQR).

	All patients	RA	PsA	SpA	JIA	UA	SLE	PAPS – aPL carriers	UCTD	pSS	SSc	IIM	SV	Anti-Ro/SSA carriers
Number of women	851	121	67	47	30	11	167	130	135	40	28	20	37	18
Age at conception (years), median (IQR)	34 (31–37)	35 (32–38)	34 (30–37.5)	33 (29.5–35.5)	29 (27–32)	33 (31–34)	34 (30–36)	35.5 (31–39)	35 (32–38)	35.5 (32–38)	35 (30–38)	32.5 (28.5–38)	33 (29–36)	33.5 (30.2–36.8)
Disease duration at enrolment (years)	6.4 (2.6–11.4)	6.7 (3.7–12.1)	6.4 (2.5–12.1)	7.4 (2.7–10)	21.6 (12.8–26.4)	5.6 (1.1–7.5)	9.3 (5.6–15.4)	2 (1–6.1)	5.2 (2.1–9.8)	5.6 (2.4–10.5)	6 (3.4–10.9)	6.3 (3.2–14.1)	6.8 (4.8–12.2)	2.9 (1.2–4.9)
Missing	29 (3.4%)	1 (0.8%)	2 (3%)	1 (2.1%)	0 (0%)	0 (0%)	7 (4.2%)	6 (4.6%)	5 (3.7%)	2 (5%)	2 (7.1%)	0 (0%)	2 (5.4%)	1 (5.6%)
BMI at enrolment (kg/m^2)	22.5 (20.3–25.2)	22.5 (20.3–25.4)	24 (21–27.4)	23.5 (20.4–26.4)	22 (20.3–23.7)	22.9 (21.8–25.2)	22.5 (20.2–25.4)	23 (20.9–26.1)	22 (20.1–23.7)	21 (19.6–23.2)	23.1 (21.3–24.7)	22.3 (19.8–24.4)	22.2 (19.9–25.6)	21.9 (20.1–24.6)
BMI>30 at enrolment	74 (8.7%)	11 (9.1%)	14 (20.9%)	6 (12.8%)	1 (3.3%)	0 (0%)	11 (6.6%)	12 (9.2%)	7 (5.2%)	2 (5%)	1 (3.6%)	1 (5%)	5 (13.5%)	3 (16.7%)
Missing	34 (4%)	4 (3.3%)	0 (0%)	1 (2.1%)	1 (3.3%)	0 (0%)	5 (3%)	6 (4.6%)	8 (5.9%)	3 (7.5%)	2 (7.1%)	0 (0%)	1 (2.7%)	3 (16.7%)
Ethnicity														
Caucasian	757 (89%)	100 (82.6%)	64 (95.5%)	43 (91.5%)	27 (90%)	10 (90.9%)	140 (83.8%)	121 (93.1%)	122 (90.4%)	38 (95%)	26 (92.9%)	15 (75%)	35 (94.6%)	16 (88.9%)
Afro-American	19 (2.2%)	5 (4.1%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	3 (1.8%)	2 (1.5%)	5 (3.7%)	1 (2.5%)	0 (0%)	2 (10%)	0 (0%)	0 (0%)
Asian	20 (2.4%)	4 (3.3%)	0 (0%)	3 (6.4%)	0 (0%)	1 (9.1%)	9 (5.4%)	1 (0.8%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.6%)
Latin-American	25 (2.9%)	3 (2.5%)	1 (1.5%)	0 (0%)	3 (10%)	0 (0%)	6 (3.6%)	4 (3.1%)	4 (3%)	1 (2.5%)	0 (0%)	2 (10%)	0 (0%)	1 (5.6%)
Arabic	27 (3.2%)	6 (5%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	9 (5.4%)	2 (1.5%)	3 (2.2%)	0 (0%)	2 (7.1%)	1 (5%)	2 (5.4%)	0 (0%)
Other	3 (0.4%)	3 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Obstetric history														
Use of female contraceptive methods (ever)	283 (33.2%)	34 (27.9%)	26 (37.7%)	15 (31.9%)	10 (32.3%)	1 (8.3%)	39 (23.1%)	59 (43.7%)	43 (31.6%)	15 (36.6%)	10 (35.7%)	9 (45%)	17 (44.7%)	5 (27.8%)
Missing	235 (27.6%)	36 (29.5%)	15 (21.7%)	12 (25.5%)	11 (35.5%)	5 (41.7%)	54 (32%)	30 (22.2%)	38 (27.9%)	12 (29.3%)	4 (14.3%)	4 (20%)	10 (26.3%)	4 (22.2%)
Primigravida	355 (41.7%)	53 (43.8%)	29 (43.2%)	23 (48.9%)	17 (56.6%)	6 (54.5%)	82 (49.1%)	26 (20%)	51 (37.8%)	18 (45%)	13 (46.4%)	11 (55%)	20 (54.1%)	6 (33.3%)
Previous live birth*	337/489 (68.9%)	51/67 (76.1%)	28/38 (73.7%)	14/23 (60.9%)	11/12 (91.7%)	5/5 (100%)	58/84 (69%)	61/102 (59.8%)	51/84 (60.7%)	15/22 (68.2%)	12/15 (80%)	8/9 (88.9%)	14/16 (87.5%)	9/12 (75%)
Previous miscarriage*	278/489 (56.9%)	25/67 (37.3%)	21/38 (55.3%)	15/23 (65.2%)	3/12 (25%)	3/5 (60%)	41/84 (48.8%)	82/102 (80.4%)	50/84 (59.5%)	14/22 (63.6%)	8/15 (53.3%)	2/9 (22.2%)	7/16 (43.8%)	7/12 (58.3%)

Continued

Table 2 Continued

	All patients	RA	PsA	SpA	JIA	UA	SLE	PAPS – aPL carriers	UCTD	pSS	SSc	IIM	SV	Anti-Ro/SSA carriers
Missing data on previous pregnancies	7 (0.8%)	1 (0.8%)	0 (0%)	1 (2.1%)	1 (3.3%)	0 (0%)	1 (0.6%)	2 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.7%)	0 (0%)

*Both previous live birth and miscarriage were experienced by 130/489 (26.6%) women.
aPL, antiphospholipid antibodies; BMI, body mass index; EC, eclampsia; EQ-5D-3L, EuroQoL questionnaire (score range: −1.6: poorest quality of life; 1: excellent quality of life); GW, gestational week; HELLP, Haemolysis, Elevated Liver enzymes, Low Platelets; IIM, idiopathic inflammatory myopathies; IUGR, intrauterine growth restriction; JIA, juvenile idiopathic arthritis; PAPS, primary antiphospholipid syndrome; PE, pre-eclampsia; PGA, Physician Global Assessment; PsA, psoriatic arthritis; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis.

Figure 3 Illustration of number of patients, pregnancies and neonates included in the analysis, presented on maternal diagnosis of autoimmune rheumatic disease. *Non-viable pregnancies*: A: pregnancy loss ≤10 GW; B: pregnancy loss 11–20 GW; C: pregnancy loss >20 GW; D: elective termination of pregnancy. anti-Ro/SSA, asymptomatic carriers of anti-Ro/SSA antibodies; GW, gestational week; IIM, idiopathic inflammatory myopathies; JIA, juvenile idiopathic arthritis; PAPS - aPL, primary antiphospholipid syndrome and antiphospholipid antibody carriers; PsA, psoriatic arthritis; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SSc, systemic sclerosis; SV, systemic vasculitis; UA, undifferentiated arthritis; UCTD, undifferentiated connective tissue disease.

Table 3 Characteristics, complications and outcomes of pregnancies. Categorical variables are expressed as numbers (percentages) and continuous variables as median (IQR).

	All pregnancies	RA	PsA	SpA	JIA	UA	SLE	PAPS – aPL carriers	UCTD	pSS	SSc	IIM	SV	Anti-Ro/SSA carriers
Number of pregnancies	866	122	69	47	31	12	169	135	136	41	28	20	38	18
Gestational week at enrolment	11 (8–15)	10 (8–14)	10 (7–13)	11 (8–14)	11 (7–14.5)	11 (9–16)	9 (7–14)	11 (8–15)	12 (9–15)	12 (10–15)	11 (9–16)	11.5 (9–16)	10.5 (8.2–14)	12.5 (8.2–17)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Time to spontaneous pregnancy (months)	3 (1–8)	2 (0–6)	4 (1–8)	3 (1.2–5)	2 (0–5.8)	3.5 (2.2–4)	3 (0–9)	3 (1–8)	3 (0–8.8)	4 (2–6)	2.5 (1–5.2)	2 (1–4.2)	2 (0.5–8.5)	0 (0–12)
Missing	185 (21.4%)	18 (14.8%)	6 (8.7%)	13 (27.7%)	5 (16.1%)	2 (16.7%)	35 (20.7%)	28 (20.7%)	38 (27.9%)	12 (29.3%)	8 (28.6%)	4 (20%)	11 (28.9%)	5 (27.8%)
Pregnancy induced by ARTs	53 (6.1%)	8 (6.6%)	2 (2.9%)	3 (6.4%)	0 (0%)	0 (0%)	11 (6.5%)	13 (9.6%)	11 (8.1%)	1 (2.4%)	2 (7.1%)	0 (0%)	1 (2.6%)	1 (5.6%)
Missing	7 (0.8%)	0 (0%)	0 (0%)	2 (4.3%)	0 (0%)	0 (0%)	0 (0%)	2 (1.5%)	2 (1.5%)	0 (0%)	0 (0%)	0 (0%)	1 (2.6%)	0 (0%)
Spontaneous miscarriage	61 (7%)	15 (12.3%)	7 (10.1%)	1 (2.1%)	1 (3.2%)	1 (8.3%)	13 (7.7%)	11 (8.1%)	6 (4.4%)	2 (4.8%)	1 (3.6%)	0 (0%)	2 (5.2%)	1 (5.6%)
≤10 GW	33 (3.8%)	8 (6.6%)	5 (7.3%)	1 (2.1%)	1 (3.2%)	0 (0%)	7 (4.1%)	7 (5.2%)	1 (0.7%)	1 (2.4%)	0 (0%)	---	1 (2.6%)	1 (5.6%)
11–20 GW	20 (2.3%)	4 (3.3%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	5 (3%)	3 (2.2%)	4 (3%)	1 (2.4%)	1 (3.6%)	---	1 (2.6%)	0 (0%)
>20 GW	8 (0.9%)	3 (2.4%)	1 (1.4%)	0 (0%)	0 (0%)	1 (8.3%)	1 (0.6%)	1 (0.7%)	1 (0.7%)	0 (0%)	0 (0%)	---	0 (0%)	0 (0%)
GW at pregnancy loss	9.9 (8.4–13)	9.4 (8.6–13)	9.9 (7.6–11.4)	10	5.9	24.4	9.7 (9–11.6)	9.4 (8.6–12)	15.2 (11.3–17.5)	9.1 (8.2–10)	12.7	---	9.9 (8.1–11.6)	9
ETOP	11 (1.3%)	2 (1.6%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	4 (2.4%)	1 (0.7%)	1 (0.7%)	0 (0%)	1 (3.6%)	1 (5%)	0 (0%)	0 (0%)
Due to malformation	1 (0.1%)	0 (0%)	1 (1.4%)	---	---	---	0 (0%)	0 (0%)	0 (0%)	---	0 (0%)	0 (0%)	---	---
Due to other reasons	10 (1.2%)	2 (1.6%)	0 (0%)	---	---	---	4 (2.4%)	1 (0.7%)	1 (0.6%)	---	1 (3.6%)	1 (5%)	---	---
GW at ETOP	13 (9.2–16)	11.1 (11–11.2)	14.1	---	---	---	8.6 (7.6–12.4)	16	22.6	---	21	7.4	---	---
Maternal disease flares during pregnancy	135 (15.6%)	27 (22.1%)	18 (26.1%)	7 (14.9%)	8 (25.8%)	3 (25%)	28 (16.6%)	12 (8.9%)	12 (8.8%)	4 (9.8%)	5 (17.9%)	3 (15%)	5 (13.2%)	3 (16.7%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pregnancy complications (≥1 complication)*	261 (30.1%)	38 (31.1%)	13 (18.8%)	12 (25.5%)	4 (12.9%)	4 (33.3%)	64 (37.9%)	47 (34.8%)	39 (28.7%)	8 (19.5%)	7 (25%)	4 (20%)	14 (36.8%)	7 (38.9%)
Congenital heart block	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.6%)
Live birth	794 (91.7%)	105 (86.1%)	61 (88.4%)	46 (97.9%)	30 (96.8%)	11 (91.7%)	152 (89.9%)	123 (91.1%)	129 (94.9%)	39 (95.1%)	26 (92.9%)	19 (95%)	36 (94.7%)	17 (94.4%)

Continued

Table 3 Continued

	All pregnancies	RA	PsA	SpA	JIA	UA	SLE	PAPS – aPL carriers	UCTD	pSS	SSc	IIM	SV	Anti-Ro/SSA carriers
GW at delivery	38.6 (37.6–39.6)	38.9 (38.1–39.6)	39.1 (38.4–40.1)	40.1 (39.1–41)	39.6 (39.1–40.2)	40 (37.2–40.1)	38.6 (36.6–39.6)	38.5 (37.6–39.2)	39 (38–40)	39 (38–39.6)	39 (37.6–40)	38.6 (38.1–40)	39.1 (38.4–40)	38.4 (37.1–39.4)
Missing GW at delivery	10 (1.2%)	1 (0.8%)	4 (5.8%)	1 (2.1%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.8%)	0 (0%)	0 (0%)	1 (3.8%)	1 (5.3%)	0 (0%)	0 (0%)
Term birth (beyond 37 GW)	674/794 (84.9%)	92/105 (87.6%)	54/61 (88.5%)	42/46 (91.3%)	29/30 (96.7%)	8/11 (72.7%)	124/152 (81.6%)	103/123 (83.7%)	111/129 (86%)	32/39 (82%)	20/26 (77%)	16/19 (84.2%)	36/36 (100%)	13/17 (76.5%)
Preterm birth (34–36.6 GW)	82/794 (10.3%)	9/105 (8.6%)	0 (0%)	2/46 (4.4%)	1/30 (3.3%)	1/11 (9.1%)	18/152 (11.8%)	16/123 (13.1%)	17/129 (13.2%)	7/39 (18%)	5/26 (19.2%)	2/19 (10.5%)	0 (0%)	4 (23.5%)
Severe preterm birth (28–33.6 GW)	17/794 (2.1%)	3/105 (2.8%)	2/61 (3.3%)	0 (0%)	0 (0%)	1/11 (9.1%)	7/152 (4.6%)	3/123 (2.4%)	1/129 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Very severe preterm birth (<28 GW)	9/794 (1.1%)	1/105 (0.9%)	2/61 (3.3%)	1/46 (2.2%)	0 (0%)	1/11 (9.1%)	3/152 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Delivery mode	n=794	n=105	n=61	n=46	n=30	n=11	n=152	n=123	n=129	n=39	n=26	n=19	n=36	n=17
Spontaneous vaginal	270 (31.2%)	35 (33.4%)	27 (44.3%)	16 (34.8%)	15 (50%)	5 (45.4%)	35 (23%)	32 (26%)	50 (38.8%)	16 (41%)	9 (34.7%)	8 (42.1%)	12 (33.3%)	10 (58.8%)
Induced vaginal	176 (20.3%)	26 (24.8%)	8 (13.1%)	10 (21.7%)	5 (16.6%)	1 (9.1%)	35 (23%)	36 (29.3%)	31 (24%)	5 (12.8%)	7 (26.9%)	4 (21.1%)	4 (11.1%)	4 (23.5%)
Operative vaginal	17 (2%)	1 (0.9%)	1 (1.6%)	2 (4.3%)	1 (3.3%)	1 (9.1%)	2 (1.3%)	0 (0%)	2 (1.6%)	3 (7.7%)	0 (0%)	1 (5.3%)	3 (8.3%)	0 (0%)
C-section for emergency reasons	120 (13.9%)	17 (16.2%)	8 (13.1%)	9 (19.6%)	2 (6.7%)	2 (18.2%)	33 (21.7%)	16 (13%)	12 (9.3%)	9 (23.1%)	4 (15.4%)	2 (10.5%)	5 (14%)	1 (5.9%)
Elective C-section for obstetric decision	140 (16.2%)	16 (15.2%)	12 (19.7%)	4 (8.7%)	3 (10%)	2 (18.2%)	36 (23.7%)	30 (24.4%)	19 (14.7%)	4 (10.3%)	4 (15.4%)	2 (10.5%)	6 (16.7%)	2 (11.8%)
Elective C-section due to podalic presentation	26 (3%)	6 (5.7%)	1 (1.6%)	1 (2.2%)	2 (6.7%)	0 (0%)	5 (3.3%)	3 (2.4%)	4 (3.1%)	0 (0%)	1 (3.8%)	0 (0%)	3 (8.3%)	0 (0%)
Elective C-section due to patient's preference	26 (3%)	2 (1.9%)	2 (3.3%)	1 (2.2%)	2 (6.7%)	0 (0%)	5 (3.3%)	4 (3.3%)	7 (5.4%)	0 (0%)	0 (0%)	0 (0%)	3 (8.3%)	0 (0%)
Missing	19 (10.5%)	2 (1.9%)	2 (3.3%)	3 (6.5%)	0 (0%)	0 (0%)	1 (0.7%)	2 (1.6%)	4 (3.1%)	2 (5.1%)	1 (3.8%)	2 (10.5%)	0 (0%)	0 (0%)
Perinatal death	4/794 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4/152 (2.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*See online supplemental table 5 for details.
ARTs, assisted reproduction techniques; C-section, caesarean section; ETOP, elective termination of pregnancy; GW, gestational week; IIM, idiopathic inflammatory myopathies; JIA, juvenile idiopathic arthritis; PAPS, primary antiphospholipid syndrome; PsA, psoriatic arthritis; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SSc, systemic sclerosis; SV, systemic vasculitis; UA, undifferentiated arthritis; UCTD, undifferentiated connective tissue disease.

Table 4 Neonatal outcomes (excluding perinatal deaths). Categorical variables are expressed as numbers (percentages) and continuous variables as median (IQR).

	All newborns	RA	PsA	SpA	JIA	UA	SLE	PAPS – aPL carriers	UCTD	pSS	SSc	IIM	SV	Anti-Ro/ SSA carriers
Number of newborns	790	105	61	46	30	11	148	123	129	39	26	19	36	17
GW at delivery	39 (38–40)	38.9 (38.1–39.6)	39.1 (38.4–40.1)	40.1 (39.1–41)	39.6 (39.1–40.2)	40 (37.2–40.1)	39 (37.5–40)	38.5 (37.6–39.2)	39 (38–40)	39 (38–39.6)	39 (37.6–40)	38.6 (38.1–40)	39.1 (38.4–40)	38.4 (37.1–39.4)
Newborn sex														
Male sex	382 (48.3%)	47 (44.8%)	29 (47.5%)	19 (41.3%)	13 (43.3%)	7 (63.6%)	78 (52.7%)	62 (50.4%)	64 (49.6%)	14 (35.9%)	12 (46.2%)	9 (47.4%)	21 (58.3%)	7 (41.2%)
Female sex	386 (48.9%)	56 (53.3%)	28 (45.9%)	25 (54.3%)	15 (50%)	2 (18.2%)	67 (45.3%)	60 (48.8%)	64 (49.6%)	23 (59%)	13 (50%)	9 (47.4%)	14 (38.9%)	10 (58.8%)
Missing	22 (2.8%)	2 (1.9%)	4 (6.6%)	2 (4.3%)	2 (6.7%)	2 (18.2%)	3 (2%)	1 (0.8%)	1 (0.8%)	2 (5.1%)	1 (3.8%)	1 (5.3%)	1 (2.8%)	0 (0%)
Birth weight (kilograms)	3.1 (2.8–3.4)	3.1 (2.8–3.4)	3.1 (2.9–3.3)	3.3 (3.1–3.6)	3.4 (3–3.5)	3.4 (3.3–3.8)	3 (2.6–3.4)	2.9 (2.7–3.2)	3.2 (2.8–3.4)	3.2 (2.8–3.5)	3 (2.8–3.3)	3.1 (2.8–3.4)	3.2 (3–3.5)	3.2 (2.6–3.5)
Missing	40 (5.1%)	7 (6.7%)	7 (11.5%)	1 (2.2%)	2 (6.7%)	2 (18.2%)	7 (4.7%)	5 (4.1%)	3 (2.3%)	0 (0%)	1 (3.8%)	3 (15.8%)	2 (5.6%)	0 (0%)
Birth length (cm)	49 (48–51)	49 (48–50.5)	49.5 (48–50.1)	50 (48.2–51.5)	50 (48–51)	51 (51–52)	49 (47–50)	49 (48–50)	49 (47–50)	49 (49–51.2)	50 (48.8–50.6)	50 (48–51)	49 (49–51)	49.5 (49–50)
Missing	217 (27.5%)	31 (29.5%)	13 (21.3%)	10 (21.7%)	9 (30%)	2 (18.2%)	44 (29.7%)	31 (25.2%)	38 (29.5%)	16 (41%)	6 (23.1%)	6 (31.6%)	11 (30.6%)	0 (0%)
SGA neonate	31 (3.9%)	3 (2.9%)	1 (1.6%)	1 (2.2%)	1 (3.3%)	0 (0%)	12 (8.1%)	2 (1.6%)	7 (5.4%)	1 (2.6%)	0 (0%)	2 (10.5%)	1 (2.8%)	0 (0%)
Missing	7 (0.9%)	0 (0%)	2 (3.3%)	0 (0%)	0 (0%)	0 (0%)	2 (1.4%)	0 (0%)	1 (0.8%)	0 (0%)	1 (3.8%)	1 (5.3%)	0 (0%)	0 (0%)
Congenital malformations*	16 (2%)	3 (2.9%)	0 (0%)	3 (6.5%)	1 (3.3%)	0 (0%)	3 (2%)	1 (0.8%)	4 (3.1%)	1 (2.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	34 (4.3%)	4 (3.8%)	5 (8.2%)	7 (15.2%)	1 (3.3%)	0 (0%)	4 (2.7%)	2 (1.6%)	3 (2.3%)	3 (7.7%)	1 (3.8%)	3 (15.8%)	1 (2.8%)	0 (0%)
Neonatal complications†	169 (21.4%)	28 (26.7%)	9 (14.8%)	5 (10.9%)	7 (23.3%)	0 (0%)	42 (28.4%)	19 (15.4%)	35 (27.1%)	7 (17.9%)	5 (19.2%)	4 (21.1%)	6 (16.7%)	2 (11.8%)
Missing	7 (0.9%)	0 (0%)	2 (3.3%)	0 (0%)	0 (0%)	0 (0%)	2 (1.4%)	0 (0%)	1 (0.8%)	0 (0%)	1 (3.8%)	1 (5.3%)	0 (0%)	0 (0%)
Neonatal breastfeeding in the 4 weeks after birth														
Maternal breastfeeding only	404 (46.7%)	49 (46.7%)	30 (49.2%)	27 (58.7%)	16 (53.3%)	7 (63.6%)	68 (45.9%)	69 (56.1%)	70 (54.2%)	20 (51.3%)	11 (42.3%)	8 (42.1%)	20 (55.6%)	9 (52.9%)
Formulated milk only	150 (17.3%)	25 (23.8%)	19 (31.1%)	7 (15.3%)	7 (23.3%)	2 (18.2%)	31 (21%)	17 (13.8%)	12 (9.3%)	7 (17.9%)	8 (30.8%)	4 (21%)	8 (22.2%)	3 (17.6%)

Continued

Table 4 Continued

	All newborns	RA	PsA	SpA	JIA	UA	SLE	PAPS – aPL carriers	UCTD	pSS	SSc	IIM	SV	Anti-Ro/ SSA carriers
Mixed (both maternal and formulated milk)	149 (17.2%)	19 (18.1%)	10 (16.4%)	6 (13%)	5 (16.7%)	2 (18.2%)	30 (20.3%)	24 (19.5%)	28 (21.7%)	8 (20.5%)	4 (15.4%)	4 (21%)	7 (19.4%)	2 (11.9%)
Missing	87 (11.3%)	12 (11.4%)	2 (3.3%)	6 (13%)	2 (6.7%)	0 (0%)	19 (12.8%)	13 (10.6%)	19 (14.7%)	4 (10.3%)	3 (11.5%)	3 (15.9%)	1 (2.8%)	3 (17.6%)
Positive EPDS score at 1–2 months after delivery	89/414 (21.5%)	10/46 (21.7%)	9/35 (25.7%)	5/24 (20.8%)	6/18 (33.3%)	2/8 (25%)	20/75 (26.7%)	10/67 (25.6%)	11/43 (14.9%)	7/19 (36.8%)	1/13 (7.7%)	0/9 (0%)	7/19 (36.8%)	1/12 (8.3%)
Missing	376 (47.6%)	59 (48.4%)	26 (42.6%)	22 (46.8%)	12 (40%)	3 (27.3%)	73 (49.3%)	56 (41.5%)	56 (43.4%)	20 (51.3%)	13 (50%)	10 (52.6%)	17 (47.2%)	9 (52.9%)

*Major and minor malformations included; no patterns of malformations were observed.
†Major complications (sepsis; severe respiratory distress syndrome; assisted ventilation ≥24 hours; admission to neonatal intensive care unit ≥4 days; necrotising enterocolitis; hypotonia ≥2 hours; epilepsy; severe brain haemorrhage) or minor complications (non-severe respiratory distress syndrome, hyperbilirubinaemia; perinatal infections); other complications could be added by investigators in open-ended field.
EPDS, Edinburgh Postnatal Depression Scale; GW, gestational week; IIM, idiopathic inflammatory myopathies; JIA, juvenile idiopathic arthritis; PAPS, primary antiphospholipid syndrome; PsA, psoriatic arthritis; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SGA, small for gestational age; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SSc, systemic sclerosis; SV, systemic vasculitis; UA, undifferentiated arthritis; UCTD, undifferentiated connective tissue disease.

months after delivery and 89 (21.5%) scored positive for emotional disturbances/depressive symptomatology.

Treatment during pregnancy

Regarding the use of antirheumatic drugs (table 5), 244 (28.2%) pregnancies were treated with glucocorticoids, 388 (44.8%) with hydroxychloroquine (HCQ), 85 (9.8%) with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and 122 (14.1%) with biological DMARDs (bDMARDs). Patients with CTD-SV received csDMARDs and bDMARDs during pregnancy in 13% and 2.6% of the cases, while patients with IA received these drugs in 3.9% and 38.1%, respectively. 107 (87.7%) pregnancies treated with bDMARDs belonged to the IA group. Except for one pregnancy exposed to rituximab, the remaining ones were treated with tumour necrosis factor inhibitors (TNFi), namely certolizumab pegol (CPZ) (80/106; 75.5%), etanercept (16/106; 15.1%) and adalimumab (11/106; 10.4%) (online supplemental table 6). Low-dose acetylsalicylic acid (LDASA), heparin and a combination of both were used in 506 (58.4%), 220 (25.4%) and 186 (21.5%) pregnancies, respectively. No medications (neither antirheumatic drugs, nor LDASA and/or heparin) were prescribed in 144 (16.6%) pregnancies.

DISCUSSION

This nationwide prospective cohort study was created in 2017 with the goal of systematically collecting data on prespecified outcomes of pregnancy in patients with ARD. With regular follow-up visits and detailed information on maternal disease activity, obstetrical complications, and use of medications at several time points, prospective pregnancy registers can provide a unique perspective that is complementary and additional to the information derived from administrative databases or global safety registers. This inaugural paper of the P-RHEUM.it study aims to provide an overview of the cohort and to serve as a reference for future publications focusing on the inferential analysis within single diseases.

By enrolling nearly 1300 pregnancies in 29 centres over 5 years, the P-RHEUM.it study can provide insight into several aspects of the current management of ARD during pregnancy and their impact on obstetrical and neonatal outcomes. Nearly two-thirds of enrolled patients had a diagnosis within the spectrum of CTD-SV (including rare diseases), with being SLE the most represented disease in this cohort (19.6%). Although IA such as rheumatoid arthritis (RA), PsA and spondyloarthritis (SpA) are more prevalent diseases than CTD-SV, the composition of our cohort reflects the nature of the enrolling centres, which are second-level or third-level, hospital-based rheumatology units; many centres run joint pregnancy clinics. Therefore, we may speculate that the referral of pregnant patients to specialised centres is more likely for those with CTD-SV who are perceived as at increased risk of pregnancy complications. Since 38% of the patients with IA in our cohort were treated with bDMARDs, we may also speculate that patients with IA are more likely to be referred when severe and treated with second-line drugs.

Preconception counselling and shared-decision making are the key elements when taking care of women living with ARD who wish for a pregnancy.[3] In our cohort, this approach was reflected by the condition of remission or low disease activity for most of the patients, as described by patient-reported and physician-reported outcomes. Only one-fifth of patients had a disease flare during the year prior to conception, supporting the fact that most of the patients have planned their pregnancy while on stable inactive disease, as also suggested by a median disease duration of 6.4 years prior to conception. Along with this, disease flares during pregnancy occurred in a minority of patients (15%), showing that good disease control prior to conception and during the first trimester is a protective factor against flares later in pregnancy, as already described in RA[19 20] and SLE.[21]

The use of pregnancy-compatible medications before conception is one of the pillars of preconception counselling and aims at keeping the maternal disease under control during pregnancy; inactive disease is indeed a major asset in favouring both maternal and fetal well-being.[3] Active disease was demonstrated to be strongly associated with APO; therefore, good disease control prior to and during pregnancy is the best strategy to minimise the impact of maternal disease on pregnancy outcomes.[22]

When comparing outcomes in our cohort with those of pregnancies in the Italian general obstetric population (GOP) during the same calendar years (online supplemental table 7), the frequency of spontaneous miscarriage was apparently not significantly different (7% in ARD vs 11% in GOP). However, we cannot exclude underreporting of early miscarriages in our cohort. Conversely, there is a striking difference in the frequency of previous miscarriages, which was 56.9% and 17.5% in our cohort and in GOP, respectively. The fact that one out of two non-primigravida patients had experienced at least one previous miscarriage may reflect the influence of subclinical/undiagnosed and/or untreated ARD on pregnancy outcomes.[23] Chronic disease and/or its treatment may also have influenced fertility, as pregnancies induced by ARTs were 6.1%, while they were 3.7% in GOP. On the other hand, a normal time-to-pregnancy (TTP) of 3 (IQR 1–8) months was observed, suggesting that infertility/subfertility was not a concern in our cohort. The TTP reported in the literature was longer than ours[3] and we cannot exclude underestimation, since we enrolled patients who were already pregnant and not during the preconception period.

In the present study, we restricted the analysis to singleton pregnancies, in order to assess obstetrical complications without the bias of multifetal pregnancies which are at increased risk of APO such as PE, FGR and

Table 5 Medications (antirheumatic drugs and adjunct treatment) used during pregnancy (at least one reported use in any trimester). Categorical variables are expressed as numbers (percentages) and continuous variables as median (IQR)

	All pregnancies	RA	PsA	SpA	JIA	UA	SLE	PAPS – aPL carriers	UCTD	pSS	SSc	IIM	SV	Anti-Ro/SSA carriers
Number of pregnancies	866	122	69	47	31	12	169	135	136	41	28	20	38	18
Oral Glucocorticoids	244 (28.2%)	52 (42.6%)	15 (21.7%)	6 (12.8%)	5 (16.1%)	4 (33.3%)	84 (49.7%)	15 (11.1%)	24 (17.6%)	8 (19.5%)	4 (14.3%)	12 (60%)	12 (31.6%)	3 (16.7%)
NSAIDs (regular use)	10 (1.2%)	1 (0.8%)	2 (2.9%)	4 (8.5%)	0 (0%)	1 (8.3%)	1 (0.6%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hydroxychloroquine	388 (44.8%)	59 (48.4%)	4 (5.8%)	1 (2.1%)	5 (16.1%)	3 (25%)	136 (80.5%)	40 (29.6%)	82 (60.3%)	30 (73.2%)	6 (21.4%)	10 (50%)	1 (2.6%)	11 (61.1%)
csDMARDs *	85 (9.8%)	4 (3.3%)	5 (5.8%)	1 (2.1%)	1 (3.2%)	0 (0%)	46 (27.2%)	4 (3%)	3 (2.2%)	0 (0%)	4 (14.3%)	10 (50%)	7 (18.4%)	0 (0%)
bDMARDs *	122 (14.1%)	46 (37.7%)	27 (39.1%)	17 (36.2%)	12 (38.7%)	5 (41.7%)	7 (4.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	7 (18.4%)	0 (0%)
tsDMARDs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Adjunct treatment														
LDASA	566 (58.4%)	42 (34.4%)	27 (39.1%)	14 (29.8%)	10 (32.3%)	7 (58.3%)	123 (72.8%)	115 (85.2%)	83 (61%)	22 (53.7%)	20 (71.4%)	12 (60%)	23 (60.5%)	8 (44.4%)
Heparin	220 (25.4%)	10 (8.2%)	6 (8.7%)	2 (4.3%)	1 (3.2%)	1 (8.3%)	53 (31.4%)	107 (79.3%)	23 (16.9%)	5 (12.2%)	1 (3.6%)	1 (5%)	8 (21.1%)	2 (11.1%)
Folic acid	694 (80.1%)	101 (82.8%)	53 (76.8%)	34 (72.3%)	25 (80.6%)	7 (58.3%)	136 (80.5%)	111 (82.2%)	108 (79.4%)	34 (82.9%)	24 (85.7%)	15 (75%)	32 (84.2%)	14 (77.8%)
Vitamin D	521 (60.2%)	69 (56.6%)	34 (49.3%)	25 (53.2%)	14 (45.2%)	7 (58.3%)	116 (68.6%)	78 (57.8%)	83 (61%)	27 (65.9%)	17 (60.7%)	15 (75%)	28 (73.7%)	8 (44.4%)

*See online supplemental table 6 for details.
bDMARDs, biological DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; IIM, idiopathic inflammatory myopathies; JIA, juvenile idiopathic arthritis; LDASA, low-dose acetylsalicylic acid; NSAIDs, non-steroidal anti-inflammatory drugs; PAPS, primary antiphospholipid syndrome; PsA, psoriatic arthritis; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; SSc, systemic sclerosis; SV, systemic vasculitis; tsDMARDs, targeted synthetic DMARDs; UA, undifferentiated arthritis; UCTD, undifferentiated connective tissue disease.

PTB.[24] PE deserves a special comment, because it carries a high risk of irreversible maternal and fetal damage and has been reported to occur more frequently in pregnant women with ARD than GOP.[3] LDASA was proved to be an effective preventative treatment in GOP at risk of PE.[25] Therefore, rheumatology scientific societies elaborated the recommendation of offering LDASA to women with ARD at increased risk of PE, particularly those with lupus nephritis, antiphospholipid syndrome or carriers of a high-risk aPL profile.[5 6 26] LDASA seems to be also beneficial in preventing other complications such as FGR and PTB[27]; therefore, the use in pregnant women with ARD may go beyond the current recommendations, as suggested by the fact that nearly 6 out 10 patients in our cohort were on LDASA during pregnancy. The widespread use of LDASA in our cohort may have contributed to the overall low frequency of PE (2.3%) that is in line with GOP data reported in the literature (5.3%, range 1.8–9.3)[28]; however, it must be acknowledged that the assessment of the real incidence of PE is hindered by many factors, and no nationwide Italian data are available up to now. The heterogeneous approach to the use of LDASA in our cohort reflects the current debate in rheumatology on whether all patients should be treated or only selected groups.[29–32]

One of the highlights of this study is the high proportion of live births (91.7%), the majority of whom were born at term (84.9%). The frequency of congenital malformations and SGA newborns was not substantially different from GOP. This information is relevant to patients because they usually want to know if there is a good chance of having 'a baby in hands' who is not affected by prematurity and other major problems. We may speculate that this high proportion of live births, reported also by other European pregnancy registries for SpA,[33] SLE[34] and primary Sjögren's syndrome,[35] is the tangible output of modern rheumatology management applied to pregnant patients. The use of HCQ during pregnancy was widespread in most ARD included in our cohort, reaching the highest frequency in SLE (80.5%), as per international recommendations.[5 6] csDMARDs were taken during pregnancy by 1 out 10 patients, particularly those with SLE and idiopathic inflammatory myopathies. This suggests that pregnant women were treated as if they were not pregnant with regard to pregnancy-compatible medications.[36] The biggest change in management can actually be seen for TNFi. As a consequence of the initial cautious approach of discontinuing TNFi at the beginning of pregnancy, an increased risk of maternal flares and APO was observed in patients with SpA and RA.[37 38] Based on increasing safety data about the use of TNFi during pregnancy,[6 7] clinicians have progressively gained confidence using TNFi during pregnancy more liberally.[36 39 40] Particularly, CPZ was the most used TNFi in our cohort, due to its demonstrated lack of transplacental passage,[41] that allows maternal treatment throughout pregnancy without any potential impact on the immunocompetence of the neonate. Another advantage of using TNFi during pregnancy is the chance for reducing or stopping glucocorticoids, which may in turn facilitate PTB[42] and serious maternal and neonatal infections.[43] Glucocorticoids were used in less than one-third of our patients, which is a testament to both the awareness about the risk of adverse effects during pregnancy and the practice of aiming at steroid-free disease remission.

Despite the encouraging results in terms of live births, a higher frequency of PTB (13.5%) as compared with GOP (6.3%) must be acknowledged. Severe PTB (3.2%) was also more frequent than in GOP (1.6%) and accounted for three out of four perinatal deaths. The frequency of spontaneous vaginal delivery was much lower than in GOP (31.2% vs 63.1%), probably due to the common practice of inducing delivery at 40 GW in women with ARD (20.3% in our cohort) to minimise the risk of oligohydramnios and/or sudden fetal death due to acute placental failure in the post-term. Reassuringly, the proportions of both elective and emergent C-section were similar to GOP.

The puerperium is a delicate period, especially for women with ARD who may experience intense disease flares.[44] Breast feeding is universally encouraged and women with ARD should be allowed to carry it out by receiving compatible medications.[7] Nearly half of the patients in our cohort breast fed in the first month after delivery (similarly to GOP), meaning that they had received adequate counselling and were able to make an informed decision about breast feeding.

The P-RHEUM.it study was the first national registry in which emotional well-being after delivery was investigated by means of EPDS, a simple and rapid-to-score tool that can signal whether a woman reported symptoms related to anxiety and depression that deserve further assessment. In fact, it was estimated that scoring positive at EPDS is associated with a pooled risk of postpartum depression (PPD) of 27.5% (95% CI 17.8 to 37.3).[45] In our cohort, one-fifth of patients who compiled the EPDS at the postpartum visit scored positive, showing that PPD should be ruled out in a non-negligible proportion of patients with ARD. Similarly, a Mexican study found that 26.9% of women with ARD scored positive at EPDS.[46] A population-based study in the USA estimated a slightly increased risk of PPD in women with SpA/PsA/RA as compared with controls, with PPD being diagnosed in 17.2% of patients.[47] Emotional distress and PPD should not be overlooked in patients with ARD and measures should be implemented in order to minimise the impact on baby–mother bonding and parenting ability.

Strengths, limitations and future perspectives

The value of P-RHEUM.it study lies in capturing the real-world experience from numerous centres all over the country and showing the impact of modern management of ARD on antenatal and postnatal outcomes. The proportion of missing data was low for most of the collected items, demonstrating the dedicated work of investigators despite the breakout of the COVID-19 pandemic in the

middle of the enrolment period. Further analysis will yield valuable information not only on general issues regarding reproductive health and pregnancy, but also on less investigated topic such as PROs during pregnancy, frequency and implications of PPD and health conditions of infants up to 2 years of age. These peculiar features will advance the field by incorporating patients' perspectives, which is relevant for identifying unmet needs and envision interventions to improve the care of pregnant patients.[48]

The main limitation of the study is the generalisability of findings. This can be due to several reasons: (1) the study population comprised women who were mostly Caucasian and lived in a developed country that provides universal healthcare through a state-funded national health system; (2) enrolling centres were hospital-based, therefore there might be a referral bias towards more severe and/or complex patients; (3) patients with organ involvement and/or damage are generally discouraged from getting pregnant, thus no patients with severe chronic renal insufficiency, pulmonary arterial hypertension and other severe manifestations happened to be enrolled, limiting our ability to provide information about these particular situations; (4) pregnancies in some rare diseases were very few, hindering the possibility to provide meaningful information.

This first descriptive analysis of the P-RHEUM.it study paves the way to a kaleidoscope of studies that will address different topics within each disease and/or disease groups and provide answers to the current unmet needs in the management of pregnancy in ARD. The study also collected all the relevant variables according to EULAR recommendations,[11] laying the foundations for future collaborations within the EuNeP (European Network of Pregnancy Registers in Rheumatology) network[10] and other prospective studies, with the ultimate goal of reaching meaningful numbers and power of the analyses.[49]

CONCLUSION

Over decades, 'Reproductive Rheumatology' has tackled research in a sensitive field. It has been highly challenging to perform randomised clinical trials in pregnant women, because of regulatory issues, difficulty in getting dedicated funding and the need for a multicentre international approach to reach sufficient numbers. As a consequence, there is a lack of unbiased, rigorous studies that can drive clinical decisions. Prospective studies and registries have contributed to filling the gap, showing that pregnancy is possible in women with ARD and discussion about it should be embraced rather than discouraged.

The P-RHEUM.it study has captured the real-world experience in the management of pregnancy in a large cohort of women with different ARD. Maternal and neonatal outcomes were overall good, suggesting that a set of measures can work as a 'toolkit' in the approach to pregnancy. These measures include multidisciplinary preconception counselling and pregnancy monitoring, and individual risk stratification for a tailored approach that aims at inactive disease while on pregnancy-compatible medications. The most sensitive indicator of the effectiveness of these interventions is the alignment of the frequency of most complications and outcomes to that of the GOP. This can be an important reassuring message to women with ARD, as well as a strong incentive to comply with treatment and monitoring plan in order to minimise the impact of the disease on pregnancy outcomes.

However, there is still much to be addressed to improve the reproductive journey of women with ARD. The P-RHEUM.it study will dissect disease-specific issues to better understand the impact of current rheumatology management and to plan for additional interventions and/or changes in practice. It will also bring the emotional well-being of the patient into the spotlight by analysing the QoL and the risk of mental health distress, along with data about children's conditions in the first 2 years of life, which is a frequently-asked-question by the patients.

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