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Reproductive issues in lupus, antiphospholipid syndrome and other autoimmune rheumatic diseases: highlights from Rheumapreg2023

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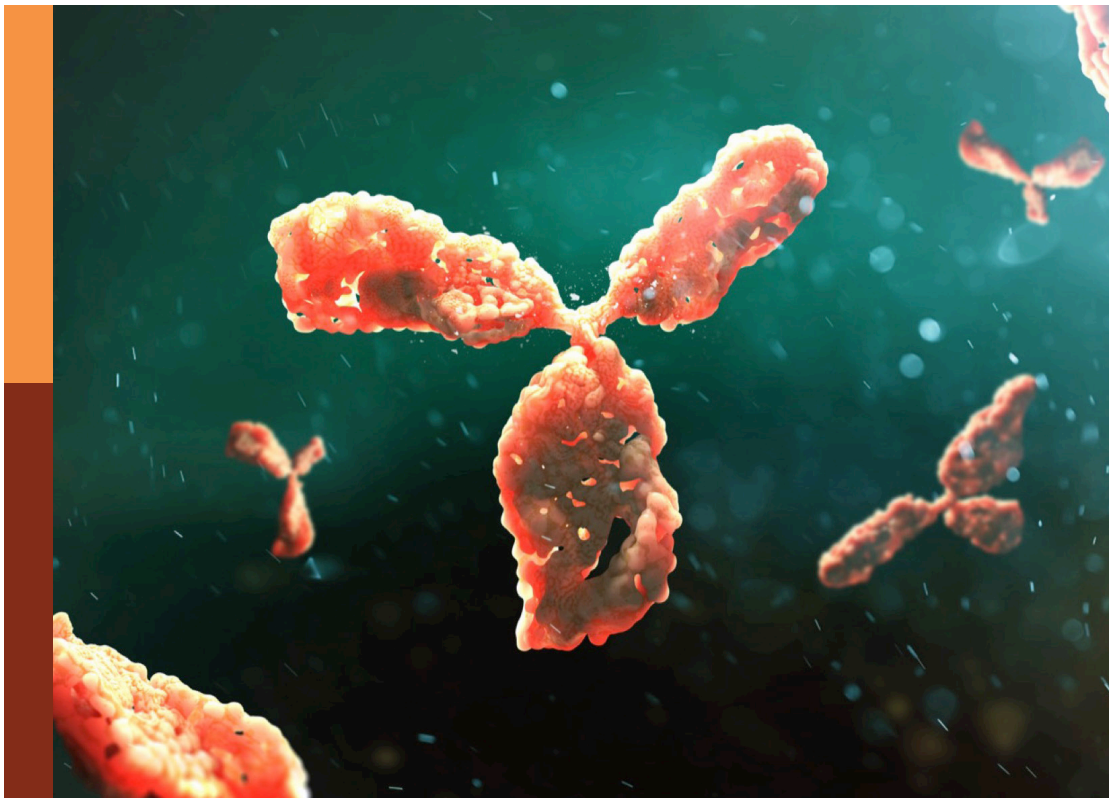

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Reproductive issues in lupus, antiphospholipid syndrome and other autoimmune rheumatic diseases: highlights from Rheumapreg2023

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Preterm birth, preeclampsia, gestational hypertension and offspring birth weight in women with active juvenile idiopathic arthritis and healthy controls

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Objectives: There is insufficient knowledge about pregnancy outcomes in women with juvenile idiopathic arthritis (JIA). Our objective was to explore a possible association of inflammatory active JIA and pregnancy outcomes, including preterm birth, preeclampsia, gestational hypertension, and offspring gestational weight.
Methods: We linked data from the Norwegian nationwide observational register RevNatus with data from the Medical Birth Registry of Norway (MBRN) for the period 2010 to 2019. Singleton births in women with JIA ($n = 181$) included in RevNatus were cases. After excluding births in mothers with rheumatic inflammatory diseases, the remaining singleton births registered in MBRN, served as population controls ($n = 575\,798$).
Results: Preterm birth was more frequent in women with active JIA (17.6%) and of equivalent frequency in women with inactive JIA (3.1%), compared to population controls (4.9%). Preeclampsia had similar rates in women with JIA and population controls while gestational hypertension was more frequent in women with active JIA (7.2%) and inactive JIA (6.9%) compared to population controls (1.7%). Abnormal fetal growth occurred in similar rates in women with JIA and population controls.
Conclusion: Having active JIA in pregnancy increased the risk for preterm birth (risk difference 12.7, 95% CI 4.7 to 25.3) and gestational hypertension (risk difference 6.2, 95% CI 1.4 to 16.8). There was no increased risk for preeclampsia or abnormal fetal growth compared to population controls.

KEYWORDS

juvenile idiopathic arthritis, inflammation, pregnancy and rheumatic disease, epidemiology, women's health

1 Introduction

Juvenile idiopathic arthritis (JIA) is the most frequent chronic rheumatic disease in childhood, emerging before 16 years of age (1). It has a heterogenous clinical presentation divided into seven subgroups and affects more girls than boys. A Nordic study reported an incidence of 15 per 100,000 children per year with a median age at

onset of 5.5 years (2). Persistent active disease was reported in 53% in early adulthood, on or off medication (3).

Preterm birth is defined as a live birth before 37 weeks of gestation and occurs in approximately 10% of births globally and in close to 6% of births in the Nordic countries (4). Preterm births may be spontaneous or initiated (5). Risk factors for spontaneous preterm birth include higher maternal age, obesity, smoking, maternal stress, earlier preterm birth and intra-amniotic infection or inflammation (6). The decision for initiating preterm birth through induction of labor or caesarean section may be due to one or several factors including maternal comorbidities, obstetric history, and psychosocial factors. In high-income countries most children born preterm reach adulthood. A concern is the association of early adulthood mortality with both early and late preterm birth for cardiovascular and other diseases (4).

Preeclampsia is a hypertensive disorder of pregnancy affecting 2% to 8% of pregnant women around the world and is the cause of substantial maternal and perinatal morbidity and mortality (7). The definition of preeclampsia has changed the last years. Traditionally new-onset hypertension and proteinuria after gestational week 20 were both compulsory findings, while it has later been defined as new onset preeclampsia-associated signs also in the absence of proteinuria (7, 8). In Norway, the prevalence has decreased over two decades, to 2.7% in 2015–2018. A gradual increase in labor induction and aspirin use may have altered the prevalence (9). The revised two-stage placental model of preeclampsia suggest that both early- (<34 gestational weeks) and late-onset preeclampsia (≥34 gestational weeks) result from placental syncytiotrophoblast stress eventually leading to the clinical stage including new-onset hypertension, renal or other organ dysfunction as well as growth restriction of the fetus (8). It incorporates known risk factors for preeclampsia like higher maternal age, nulliparity, diabetes, chronic hypertension, obesity, assisted reproduction, twin pregnancy and some chronic autoimmune diseases that may increase the risk for or accelerate the development of the clinical stage (8).

Abnormal fetal growth resulting in small for gestational age (SGA) is mostly a concern in early-onset preeclampsia. Both SGA and large for gestational age (LGA) are being discussed as risk factors for the growing child and adult life (10). There is increasing evidence that preterm birth, preeclampsia, and abnormal fetal growth increase the risk for maternal cardiovascular disease later in life (11).

Literature on pregnancy outcomes in women with JIA is limited. Three recent European studies (12–14), three American studies (15–17) and one Australian study (18) reported increased risk for preterm birth in women with JIA. Three of the studies also found an increased risk for preeclampsia (14, 15, 18), but only one study found an increased risk for SGA (14). Active disease, medication use or the disease itself are potential causes of the increased risk for pregnancy complications. In one study preterm births occurred in women with disease flares, as defined by increased clinical disease activity prompting intensified therapy (13). Another study reported disease activity based on a patient activity scale (17), and did not find an association with disease activity. The other studies did not have disease activity assessments during pregnancy.

In this study we aimed to explore the possible associations of active disease with preterm birth, preeclampsia, gestational hypertension, and offspring birth weight in women with JIA.

2 Materials and methods

2.1 Study population

Data from the RevNatus register and the Medical Birth Registry of Norway (MBRN) were linked in this population-based cohort.

RevNatus is a Norwegian nationwide medical quality register operated by The Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases (NKSR). Women with inflammatory rheumatic diseases are prospectively followed from the time of planning a pregnancy until one year after delivery. Female patients 16 years or older with a rheumatic diagnosis are eligible for inclusion before or during pregnancy. They are followed at the local outpatient rheumatology clinics before pregnancy, in every trimester during pregnancy and three times in the year after birth. Demographic variables, disease activity, medication, laboratory status, obstetric history, pregnancy outcome, self-reported health status and breastfeeding are recorded.

MBRN is a mandatory national health registry. It records information about maternal health preconception and during pregnancy, and complications in the mother and child in the course of pregnancy and birth. Inflammatory rheumatic disease in the mother are coded in MBRN according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (19). Data is accessible about two years after registration.

Singleton births recorded in MBRN 2010 to 2019 qualified for inclusion in the current study.

2.2 Ethics and patient involvement

A written informed consent is required before inclusion in RevNatus. The registry was approved by the Regional Committee for Medical and Health Research Ethics (REK) Mid Norway in 2006. The present study was approved by REK Mid Norway in June 2019 (2019/779/REK Midt) and July 2020 (minor change). Access to data from MBRN was granted in June 2020 (MBRN assignment PDB 2804). Two patient representatives contributed to the outline, development and dissemination plans of the project.

2.3 Variables

Patient group variables retrieved from RevNatus contained educational status and disease-specific information encompassing disease activity assessment and use of medication. Maternal variables included age, parity, smoking, body mass index (BMI), diabetes, chronic hypertension and assisted reproductive technology (ART) as well as the outcomes preeclampsia, gestational hypertension, preterm birth and z-score for birth weight in the current pregnancy. Variables were obtained from MBRN.

2.4 Disease activity assessment

The juvenile arthritis disease activity score (JADAS) could not be utilized, as it is not validated in adults with JIA. We used the Disease Activity Score with CRP (DAS28-CRP-3).The assessment is a composite score including the total tender and swollen joints among 28 joints and CRP (20). It is used in RA and other arthritis and has been validated for use in pregnant women with RA (21). The European alliance of associations for rheumatology (EULAR) has defined the four disease categories remission (<2,6), low disease activity (≥2.6 but ≤3.2), moderate disease activity (>3.2 but ≤5.1) and high disease activity (>5,1) (22). Inactive JIA was defined as DAS28-CRP-3 < 2.6 in 2nd or 3rd trimester and active JIA as DAS28-CRP-3 ≥ 2.6 in 2nd or 3rd trimester.

2.5 Outcomes

Preterm birth was defined as birth <37 weeks of gestation, with early preterm birth <34 gestational weeks and late preterm birth ≥34 weeks and <37 gestational weeks.

Preeclampsia was defined according to the MBRN definition at the time the data were collected as new onset blood pressure elevation ≥140/90 mmHg and proteinuria after gestational week 20. Gestational hypertension was defined as new onset blood pressure elevation ≥140/90 mmHg after gestational week 20 without proteinuria.

Z-score for birthweight was based on birth weight, gestational age, and sex. Small for gestational age (SGA) was defined as fetal weight <10th percentile and <2.5th percentile. Large for gestational age (LGA) was defined as fetal weight >90th percentile and >97.5th percentile.

2.6 Statistical analyses

We reported descriptive statistics for the inactive JIA group, active JIA group and population controls as well as disease related characteristics of the inactive JIA group and active JIA group. Pairwise group comparisons of the inactive JIA group with population controls, the active JIA group with the population controls and the active JIA group with the inactive JIA group were performed using independent samples *T*-test for continuous variables and the Pearson chi squared test, the Fisher's exact test or the unconditional z-pooled test (23) for dichotomous variables.

Proportions and risk differences for the main outcomes preterm birth, late preterm birth, preeclampsia, gestational hypertension, SGA and LGA were calculated comparing the inactive JIA group and active JIA group one at a time with population controls. We calculated 95% confidence intervals (CI) for risk differences using Newcombes method (24). Two-sided $p < 0.05$ were considered to represent statistical significance, and 95% confidence intervals (CI) are reported where relevant. The statistical analyses were performed using IBM SPSS Statistics for Windows, version 28.0.1, STATA MP 17, and https://www4.stat.ncsu.edu/~boos/exact/.

3 Results

There were 196 singleton births in women with JIA registered in RevNatus and MBRN during 2010 to 2019. Disease activity assessment in 3rd trimester was available in 160/196 cases. We added cases with disease activity assessment in 2nd trimester (21/36), while 15 cases did not have data. The resulting 181/196 cases (92.3%) with reported disease activity in 2nd or 3rd trimester ($n = 181$) were included in this study. Most of the women had inactive JIA, 130/181 (71.8%), while 51/181 (28.2%) had active JIA. After excluding singleton births in mothers with rheumatic inflammatory diseases according to the ICD-10 codes lined out in Supplementary Table S1, the remaining singleton births registered in MBRN during this decade ($n = 575{,}798$) served as controls.

Table 1 outlines characteristics known to influence the occurrence of preterm birth, preeclampsia, gestational hypertension, and abnormal fetal growth. Women with inactive JIA were younger and had a higher proportion of nulliparous

TABLE 1 Characteristics of controls and patient groups, reported as *n* (%) unless specified as mean (SD).

Characteristic	Population controls	Inactive JIA	Active JIA
		DAS28 < 2.6[a]	DAS28 ≥ 2.6[a]
Singleton births 2010–2019	575,798	130	51
Maternal age (years), mean (SD)	30.6 (5.1)	29.5 (4.6)*	30.7 (4.7)
<35	460,720 (80.0)	118 (90.8)*	39 (76.5)
≥35	115,077 (20.0)	12 (9.2)	12 (23.5)
Missing	0	0	0
Parity			
No children	244,354 (42.4)	67 (51.5)*	23 (45.1)
≥1 child	331,444 (57.6)	63 (48.5)	28 (54.9)
Missing	0	0	0
Smoking in pregnancy	34,237 (6.7)	4 (3.2)	4 (8.3)
Missing	67,663	4	3
BMI first trimester, mean (SD)	24.4 (4.8)	23.9 (4.2)	25.5 (5.3)
<25.0	2,61,663 (65.5)	64 (68.1)	26 (55.3)
25.0 - <30.0	1,38,056 (34.5)	30 (31.9)	21 (44.7)
≥30.0	49,167 (12.3)	8 (8.5)	12 (25.5)*
Missing	176,090	36	4
Diabetes[b]	25,924 (4.5)	5 (3.8)	4 (7.8)
Missing	0	0	0
Kidney disease, chronic	3,868 (0.7)	1 (0.8)	1 (2.0)
Missing	0	0	0
Hypertension, chronic	3,154 (0.5)	1 (0.8)	0
Missing	0	0	0
ART	20,121 (3.5)	6 (4.6)	4 (5.9)
Missing	0	0	0

JIA, juvenile idiopathic arthritis; BMI, body mass index; ART, assisted reproductive technology.
[a]In 2nd or 3rd trimester.
[b]Pregestational or gestational.
*p-value < 0.05 for patient group compared to population controls.

women compared to population controls. Women with active JIA had a higher proportion of obese women compared to population controls. There were no significant differences when comparing women with inactive JIA and women with active JIA to population controls concerning maternal age >35 years, smoking, diabetes, kidney disease, chronic hypertension, or ART.

In Table 2 disease characteristics in the two disease activity groups are described. Two thirds of the women with JIA had a high educational level. The majority were diagnosed fulfilling the International League Against Rheumatism (ILAR) classification criteria for JIA (1). Women with active JIA had longer disease duration, had more commonly erosive disease and were more often RF or CCP IgG positive compared to women with inactive JIA. A higher proportion of women with active JIA used prednisolone in pregnancy, while the use of the disease modifying medications hydroxychloroquine (HCQ), sulfasalazine (SSZ) and tumor necrosis factor inhibitors (TNFi's) were more frequent in women with inactive JIA. Most women on TNFi's stopped during 1st trimester (data not shown). Approximately half of the women with JIA irrespective of disease activity status used methotrexate and/or a TNFi before pregnancy.

Two women with inactive JIA reported use of methotrexate in 1st trimester. In the group of women with active JIA one reported use of rituximab and one use of tocilizumab in 1st trimester (data not shown).

Proportions and risk differences of the outcomes preterm birth, preeclampsia and gestational hypertension are presented in Table 3.

Preterm birth occurred more frequently in active JIA (9/51, 17.6%) than in population controls (27,955/569,812, 4.9%), with a risk difference of 12.7%. They were all late preterm. Women

TABLE 2 Clinical characteristics of patient groups, reported as *n* (%) unless specified as mean (SD).

Characteristic	Inactive JIA[a] DAS28 < 2.6	Active JIA[a] DAS28 ≥ 2.6	diff[b]
Singleton births 2010–2019	130	51	
Educational level			
Low (10–13 yrs)	37 (28.9)	16 (32.7)	3.8
High (≥14 yrs)	91 (71.1)	33 (67.3)	
Missing	2	2	
Classification criteria fulfilled[a,c]	115 (97.5)	44 (95.7)	1.8
Missing	12	5	
Disease duration, mean (SD)	19.7 (7.5)	22.7 (7.2)	3.0*
Missing	25	11	
Erosive disease	40 (37.7)	26 (59.1)	21.4*
Missing	24	7	
RF positive	4 (3.9)	10 (24.4)	20.5
Missing	27	10	
CCP IgG positive	11 (9.9)	11 (24.4)	14.5
Missing	19	6	
ANA positive	10 (9.0)	7 (16.3)	7.3
Missing	19	8	
Prednisolone in pregnancy	17 (15.5)	17 (37.8)	22.3*
Missing	20	6	
HCQ in pregnancy	9 (7.2)	1 (2.0)	5.2
Missing	5	2	
SSZ in pregnancy	14 (11.9)	2 (4.5)	7.4
Missing	12	7	
TNFi in pregnancy	23 (20.0)	5 (10.9)	9.1
Missing	15	5	
No medication pregnancy	54 (42.9)	19 (37.3)	5.6
Missing	4	0	
MTX before pregnancy	66 (64.7)	22 (59.5)	4.9
Missing	28	14	
TNFi before pregnancy	46 (45.1)	20 (54.1)	9.0
Missing	28	14	
RTX before pregnancy	1 (1.0)	1 (2.7)	1.6
Missing	28	14	
TCZ before pregnancy	0	4 (10.8)	10.8*
Missing	28	14	

JIA, juvenile idiopathic arthritis; RF, rheumatoid factor; CCP IgG, anti-cyclic citrullinated peptide; ANA, antinuclear antibodies; HCQ, hydroxychloroquine; SSZ, sulfasalazine; MTX, methotrexate; TNFi, tumor necrosis factor inhibitor; RTX, rituximab; TCZ, tocilizumab.
[a]In 2nd or 3rd trimester.
[b]diff = differences in proportions for dichotomous and mean difference for continuous variables.
[c]International League Against Rheumatism (ILAR) classification criteria.
*p-value < 0.05 for active compared to inactive disease.

TABLE 3 Preterm birth, preeclampsia and gestational hypertension, expressed as proportions and risk differences.

	Total	Preterm birth (<37 weeks)	%	Risk difference (95% CI)	p-value[b]
Population controls	5,69,812	27,955	4.9		
Active JIA[a]	51	9	17.6	12.7 (4.7 to 25.3)	**<0.001**[c]
Inactive JIA[a]	130	4	3.1	−1.8 (−3.7 to 2.7)	0.45
	Total	Late preterm birth (34 to <37 weeks)	%	Risk difference (95% CI)	p-value[b]
Population controls	5,69,812	19,919	3.5		
Active JIA[a]	51	9	17.6	14.1 (6.0 to 26.7)	**<0.001**[c]
Inactive JIA[a]	130	3	2.3	−1.2 (−2.8 to 3.1)	0.63
	Total	Preeclampsia	%	Risk difference (95% CI)	p-value[b]
Population controls	5,75,813	15,162	2.6		
Active JIA[a]	51	0	-	−2.6 (−2.7 to 4.4)	0.65[c]
Inactive JIA[a]	130	5	3.8	1.2 (−1.0 to 6.1)	0.40[c]
	Total	Gestational HT	%	Risk difference (95% CI)	p-value[b]
Population controls	5,75,813	9,644	1.7		
Active JIA[a]	51	4	7.2	6.2 (1.4 to 16.8)	**0.011**[c]
Inactive JIA[a]	130	9	6.9	5.2 (2.0 to 11.0)	**<0.001**[c]

JIA, juvenile idiopathic arthritis; Gestational HT, gestational hypertension.
[a]In 2nd or 3rd trimester.
[b]p-value for patient group compared to population controls.
[c]Fishers exact test.

with inactive JIA did not have an increased risk of preterm birth compared with population controls. One early preterm birth in week 27 occurred in a woman with inactive JIA and preeclampsia (data not shown).

There was not an increased risk for preeclampsia in women with active or inactive JIA compared with population controls. Gestational hypertension occurred more frequently in active JIA (4/51, 7.2%) and inactive JIA (9/130, 6.9%) compared to population controls (9,644/575,813, 1.7%), with a risk difference of 6.2% and 5.2%, respectively.

Table 4 shows SGA and LGA, looking both at the 10 percentile/90 percentile (z-score −1.28 to 1.28, <−1.3 and >1.3) and the 2.5 percentile/97.5 percentile (z-score −1.96 to 1.96, <−2.0 and >2.0). There were no differences in offspring of women with active or inactive JIA compared to offspring of population controls.

4 Discussion

In the present study we found an increased risk for preterm birth in women with JIA. This is in accordance with earlier studies (12–18). More importantly, we found that active JIA increases the risk for preterm birth, whereas inactive JIA does not.

TABLE 4 SGA and LGA as percentiles in offspring, expressed as proportions and risk differences.

	Total	SGA, 10 percentile	%	Risk difference (95% CI)	*p*-value[b]
Population controls	5,75,798	47,146	8.2		
Active JIA[a]	51	5	9.8	1.6 (−3.9 to 12.8)	0.61[c]
Inactive JIA[a]	130	13	10.0	1.8 (−2.3 to 8.2)	0.55
	Total	LGA, 90 percentile	%	Risk difference (95% CI)	*p*-value[b]
Population controls	5,75,798	48,794	8.5		
Active JIA[a]	51	3	5.9	−2.6) (−6.5 to 7.5)	0.80[c]
Inactive JIA[a]	130	8	6.2	−2.3 (−5.3 to 3.2)	0.43
	Total	SGA, 2.5 percentile	%	Risk difference (95% CI)	*p*-value[b]
Population controls	5,75,798	9,158	1.6		
Active JIA[a]	51	0	-	−1.6 (−1.6 to 5.4)	1.0[c]
Inactive JIA[a]	130	3	2.3	0.7 (−0.8 to 5.0)	0.47[c]
	Total	LGA, 97.5 percentile	%	Risk difference (95% CI)	*p*-value[b]
Population controls	5,75,798	13,807	2.4		
Active JIA[a]	51	1	2.0	−0.4 (−2.0 to 7.9)	1.0[c]
Inactive JIA[a]	130	1	0.8	−1.6 (−2.2 to 1.9)	0.38[c]

JIA, juvenile idiopathic arthritis.
[a]in 2nd or 3rd trimester.
[b]*p*-value for patient group compared to population controls.
[c]Fishers exact test.

Women with JIA had stable low disease activity or inactive disease in pregnancy. This has also been demonstrated in other cohorts of pregnant women with JIA the last decades (12, 13, 25–27). A possible association with active JIA in pregnancy has been investigated in two earlier studies, with conflicting results (13, 17). One study found no association between preterm birth and active disease. The authors argue that the disease activity assessment was limited as it did not include joint count and CRP and may have underestimated disease activity (17). Our findings are in alignment with a small study of 22 pregnancies (13) and provides evidence to the notion that disease activity matters.

Inactive disease was not found to be associated with preterm birth. The women with inactive JIA had a lower proportion of preterm birth compared to population controls. This might be due to tight control with a focus on disease specific as well as other risk factors and is reassuring, underpinning the importance of "treating to target" also in pregnancy, aiming for inactive disease (28).

All preterm births in women with active JIA in our study were late preterm (pregnancy weeks 34–36). This has also been reported in recent previous studies (13, 15, 17). This finding may be related to better disease control and less inflammation. In cohorts from earlier time-periods preterm birth was seen both early (<34 weeks) and late (34–36 weeks) (14), indicating less controlled disease.

Preterm birth can be divided into phenotypes such as preterm prelabor rupture of membranes (PPROM), medically indicated and spontaneous preterm birth. We did not have information about these phenotypes in our study, but one previous study found increased risk of late (pregnancy weeks 32–36) PPROM and medically indicated preterm birth in women with JIA, while spontaneous preterm birth occurred more frequently both early (pregnancy weeks 20–31) and late preterm (15). Inflammation is a key factor for both PPROM and spontaneous preterm birth (6) suggesting that inflammatory active disease in the mother can be a relevant risk factor.

We found no cases of preeclampsia in women with active JIA. However, we found two cases of gestational hypertension that might have resulted in medically indicated preterm birth. Cesarean section was not performed in these two cases, and we do not know whether they were induced or not. However, five of the remaining seven preterm births in women with active JIA had emergency cesarean section of unknown reason. In Norway active JIA may be an indication for induction of labor, and very rarely for elective cesarean section. Induction of labor due to active JIA will usually be done at gestational weeks 39–40.

Women with active JIA had a higher proportion of obesity than population controls. However, there were no preterm births in obese women with active JIA (data not shown).

In two studies, prednisolone use has been discussed as a possible marker of disease activity and a risk factor for preterm birth (12, 17). In our study, a higher proportion of women with active JIA using prednisolone in pregnancy had preterm birth compared to non-users, though not of statistical significance ($p = 0.053$). The proportions were similar for women with inactive JIA irrespective of prednisolone use, see online Supplementary Table S2. This indicates that active disease is a risk factor, irrespective of prednisolone use.

There are conflicting results concerning the risk of preeclampsia in women with JIA. A large Swedish prospective study found a strong association between JIA persisting into adulthood and preeclampsia (14), arguing that medication use and active disease were important factors, although there was no available information on these factors in the study. Two other studies have reported increased risk (15, 18). However, these data were from the era before the guidelines of tight follow up and rigorous treatment in pregnancy were implemented, with a higher proportion of women with active disease during pregnancy. Studies with no increased risk of preeclampsia (12, 13, 17) have data from a later time span with better disease control. Our patients with active JIA had low disease activity, favoring less complications.

In Norway, the prevalence of preeclampsia has gradually decreased the last 20 years (9). In 2020 preeclampsia occurred in 2.6%, with only 0.9% being preterm (29). The last maternal death due to preeclampsia was reported in 2012 (9). This is in contrast to many other countries including USA, where gestational hypertension is increasing, and maternal mortality has increased with 50% during the same time period (30). The decline in preeclampsia in Norway has happened despite a parallel increased proportion of women with risk factors for preeclampsia such as advanced age, nulliparity and use of ART (9). Autoimmune disease is another risk factor considered in the risk assessment early in pregnancy (9). Tighter follow up of patients with risk factors, and treatment with aspirin and/or labor induction when indicated, may explain low rates of preeclampsia in women with JIA.

In our study gestational hypertension was more frequent in active JIA than population controls. Two of four pregnancies with gestational hypertension in active JIA ended up as late preterm birth. A theoretical interpretation that has been discussed in a two-stage placental model of preeclampsia is that preterm birth might prevent clinical manifestations of preeclampsia to evolve (8). There was an increased risk of gestational hypertension also in women with inactive JIA. A higher proportion of nulliparous women in this group may have contributed to the increased risk.

We did not find an increased risk for SGA in offspring of our patients compared to offspring of population controls. Remaus et al. found such an association (14), probably due to less controlled disease. Our findings are reassuring and in line with the other findings of late preterm birth and no increased risk of preeclampsia.

A high proportion of women with JIA reported treatment with methotrexate before pregnancy, indicating the need for disease specific medication. The proportion of women on TNFi's preconception was also high. However, the proportion of women on pregnancy compatible medication during pregnancy was much lower, indicating undertreatment. One reason might be little documentation during the first years of the study on the use of TNFi's. A tight follow up and proper information may potentially improve outcomes by suppressing disease.

There are several risk factors for hypertensive disorders, preterm birth and abnormal fetal weight. In this study the exposure was JIA, and we did not find it relevant to adjust for the risk factors presented in Table 1, as we do not consider these variables as confounders. Risk assessment including these risk factors is performed early in pregnancy (29). In women with active JIA, obesity was more common than in population controls. Smoking was reported in small numbers in all groups. Active disease, overweight and smoking are all modifiable risk factors that should be taken into account in the preconception planning and counselling.

A major strength of this study is the disease activity assessment during pregnancy. Further, the prospective follow up, a large patient group and the linkage of two registries improves the quality.

A limitation is that there are no validated disease activity assessments for pregnant women with JIA. DAS28-CRP-3 is considered to be reliable for assessing disease activity in JIA (31). However, it does not evaluate ancles, toes and jaw, joints that may be affected in JIA. We may therefore have underestimated disease activity in some patients. We used disease activity assessment only in the second part of pregnancy and do not know how active disease early in pregnancy might impact on the evolvement of hypertensive disorders later in pregnancy. Another limitation is that we did not have access to the subtypes of JIA. Potentially, such information could shed light on possible differences in disease characteristics, disease activity, general risk factors and pregnancy complications between subtypes.

In this prospective cohort of women with JIA, active disease in the second part of pregnancy increased the risk for late preterm birth and gestational hypertension. Preeclampsia and SGA in offspring occurred in similar rates as population controls. Tight control targeting inactive disease is advocated.

Data availability statement

The datasets presented in this article are not readily available. The data cannot be shared publicly due to the requirements of the involved register holders and the general data protection regulation, to protect the privacy of individuals. Requests to access the datasets should be directed to https://www.fhi.no/en/.

Ethics statement

The studies involving humans were approved by the Regional Committee for Medical and Health Research Ethics (REK) Mid Norway. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CG: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. SL: Conceptualization, Formal Analysis, Methodology, Writing – review & editing.

KS: Conceptualization, Writing – review & editing, Supervision. MW: Conceptualization, Supervision, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/flupu.2024.1375857/full#supplementary-material

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Placental lesions in patients with antiphospholipid antibody syndrome: experience of a single tertiary-care Italian reference center

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Introduction: Abnormal placentation contributes to obstetric morbidity in antiphospholipid antibodies syndrome (APS). The placenta is the main target of antiphospholipid antibodies (aPL) in obstetric APS and is the site of dysfunctional inflammatory responses and thrombosis. Standard treatment for APS during pregnancy includes low-dose aspirin (LDA) plus low molecular weight heparin (LMWH) and, in refractory cases, hydroxychloroquine (HCQ). Recently, a systematic review of the literature identified five main pathological placental lesions in APS patients: placental infarction, decidual vasculopathy, decidual inflammation, increase of syncytial knots due to syncytiotrophoblast death, and decrease in vasculosyncytial membranes. The aims of this study were to investigate whether placental lesions associate with obstetrical outcomes in a cohort of APS patients.

Methods: 130 pregnant APS patients evaluated between 2009 and 2023 at the High-Risk Obstetrics Outpatient Clinic of San Raffaele Hospital, Milan, were enrolled. Placental samples from 25 spontaneously conceived pregnancies in APS patients were collected from January 2017 to May 2023 and analyzed.

Results: All (n = 130) patients were on LDA and 110/130 (85%) on both LDA and LMWH. Twenty-six patients (20%) also received HCQ. In these patients, signs of placental inflammation (preterm birth and preterm premature rupture of membranes) were less frequently observed. Of the 25 placental samples analyzed, 19 (76%) patients had primary APS, while 6 patients had APS secondary to SLE. All patients were treated with LDA and LMWH. In patients with concomitant systemic lupus erythematosus (SLE) or in refractory APS, HCQ was added. Histological analysis of placental tissue revealed increased syncytial knots in 17/25 (68%) placentas, decreased vasculosyncytial membranes in 11/25 (44%), infarction in 8/25 (32%), presence of macrophages

Abbreviations

APS, anti-phospholipid antibodies syndrome; SLE, systemic lupus erythematosus; Apl, antiphospholipid antibodies; aCL, anticardiolipin antibodies; aβ2GPI, anti–beta2-glycoprotein I antibodies; aPS-PT, anti-phosphatidylserine-prothrombin antibodies; LLAC, lupus like anticoagulant; BMI, body mass index; aGAPSS, adjusted global antiphospholipid syndrome score; PE, pulmonary embolism; DVT, deep venous thrombosis; IFD, intrauterine fetal death; IUGR, intrauterine growth restriction; APO, adverse pregnancy outcomes; HCQ, hydroxychloroquine; LDA, low-dosage aspirin; LMWH, low molecular weight heparin; gw, gestation week; OR, odds ratio; P, P value; CI, confidence interval; SD, standard deviation.

and decidual inflammation in 2/25 (8%), and atherosis or reduction of spiral artery remodeling in 3/25 (12%). We also observed at least two coexisting placental lesions in 12/25 (48%) placentas. In the placenta of patients treated with HCQ we did not observe any decidual inflammation at histology.

Conclusion: Placental anomalies have occurred in patients with APS despite close and optimal obstetric monitoring. It is thus tempting to speculate that HCQ may have beneficial effects on pregnancy by decreasing the risk of deciduitis in patients with APS.

KEYWORDS

pregnancy, miscarriages, antiphospholipid antibodies syndrome, placental histology, hydroxychloroquine

Key message

Pregnancies in women with Antiphospholipid Syndrome (APS) are considered high-risk and are closely associated with adverse pregnancy outcomes. Despite standard therapy with LDA and LMWH—and the addition of HCQ in selected cases—histopathological analysis of placentas from APS patients often reveals signs of maternal and fetal malperfusion.

Introduction

Antiphospholipid syndrome is an autoimmune systemic disorder characterized by vascular thrombosis and pregnancy morbidity in the presence of a persistent positivity of antiphospholipid antibodies (1).

The Revised Sapporo Classification Criteria define APS as the presence of at least one clinical and one laboratory criterion. Clinical criteria encompass vascular thrombosis (venous, arterial, or small vessel) and pregnancy morbidity (early recurrent miscarriage, fetal death, or premature birth before the 34th week due to conditions like preeclampsia/eclampsia or placental insufficiency). Laboratory criteria involve confirmed persistent positivity of lupus anticoagulant, anticardiolipin antibodies (IgG or IgM), or anti-β2GPI antibodies (IgG or IgM) (2). Recently, the classification criteria for APS have been updated by EULAR (3).

The Global APS Score (GAPSS) is commonly used to assess thrombotic and obstetric risk in APS patients and takes into account aPL profile and conventional cardiovascular risk factors (4). Obstetric APS is associated with miscarriage, IFD, IUGR, preeclampsia, and preterm delivery (5). Fetal loss is the most common complication, and obstetric APS stands as a leading, treatable cause of recurrent pregnancy loss (6, 7). Women with triple aPL positivity, history of vascular thrombosis and concomitant SLE and/or other autoimmune diseases are at higher risk for pregnancy complications (5, 8).

In obstetric APS, antiphospholipid antibodies target the placenta, essential for fetal development, leading to complications arising from abnormal placentation (9–11). APS interferes with trophoblast proliferation and viability, spiral artery remodeling, and vasculosyncytial membrane formation, resulting in maternal/fetal malperfusion (12) leading to issues such as preeclampsia and IUGR. During the transition from cytotrophoblasts to syncytiotrophoblasts, phosphatidylserine glycoprotein is exposed on the cell surface (13). In patients with APS, aPL can bind to cytotrophoblasts and the decidua. Several studies show a decrease in trophoblast proliferation within placental explants and an increase in trophoblast death, leading to more debris released as syncytial knots (14, 15). The balance of trophoblast quantity is crucial for nutrient supply to the fetus through vasculosyncytial membranes, spiral artery remodeling, and normal decidual function (16, 17). Alteration of these factors can lead to preeclampsia, suggesting a link between aPL and these pathological gestational conditions. Inflammation of the decidua in APS can be attributed to macrophages clustering around extravillous trophoblasts (18). In mice, excessive decidual inflammation may also result from classical complement cascade activation due to aPL deposition (19, 20). Complement components C3 and C5 are crucial for mediating aPL-induced thrombosis (21, 22). Complement activation often leads to hypocomplementemia in primary APS patients (23), likely acting as an intermediate step for platelet and endothelial activation. Both inflammatory and thrombotic mechanisms play a crucial role in the pathophysiology of APS. The intricate relationship between these mechanisms has been the subject of several excellent reviews, highlighting their complex interactions and combined impact on the disease process (24–26).

Five main pathological lesions characterize the placenta from APS pregnancies: placental infarction caused by spiral artery thrombosis, decidual vasculopathy characterized by atherotic changes in uterine spiral arteries and lack of remodeling by trophoblasts, inflammation of the decidua, increase in syncytial knots due to syncytiotrophoblast death, and decrease in vasculosyncytial membranes (27). These lesions can be classified according to their pathogenesis into inflammatory and vascular lesions (13). These categories can be further classified into maternal and fetal, and into acute and chronic lesions (28). Changes in the anatomy and function of the placenta, depending on the timing of the injury during pregnancy, can lead to recurrent miscarriage in the early phases, or preterm delivery, preeclampsia, and IUGR in the later phases of pregnancy.

Combination therapy with LDA and LMWH is the standard treatment during pregnancy (29) due to its capacity of improving live birth rate. Yet, 30% of patients still experience pregnancy complications (30). Additional strategies, including HCQ supplementation, have been proposed for refractory cases, exhibiting promise in reducing pregnancy loss and complications in selected patients (31, 32).

HCQ indeed has multifaceted beneficial effects on pregnancy complications, including anti-aggregant, anti-inflammatory, and immune-regulatory properties. It diminishes aPL binding to syncytiotrophoblasts (33–35). Additionally, HCQ safeguards pregnancy by inhibiting complement activation in the placenta (36). Sciascia et al. (32) associated HCQ treatment with reduced pregnancy complications in aPL-positive patients. However, whether HCQ treatment improves the main pathological lesions in the placenta from APS pregnancies remains to be elucidated. Moreover, it is not completely clear whether these placental abnormalities associate with specific pregnancy outcomes. Therefore, the aims of this study were to assess the presence of placental lesions in the placentas collected from APS patients, to investigate whether HCQ treatment protects against abnormal placentation, and to determine the impact of APS-related placental lesions on fetal growth and development, including the incidence of preeclampsia, IUGR and preterm delivery.

Materials and methods

Population

We performed a monocentric prospective observational study of pregnancies in women with a diagnosis of APS according to the Sapporo criteria (2). We included also patients with at least two abortions in the presence of a low titer of aPL. Data were collected from 130 pregnancies involving 96 APS patients who were followed at the High-Risk Obstetrics Outpatient Clinic of San Raffaele Hospital in Milan, Italy, from 2009 to May 2023. All pregnancies were closely monitored from conception to the post-partum clinical examination (40 days after delivery). Early miscarriage was defined as fetal loss before 10 gestational weeks, while late miscarriage was identified as fetal loss occurring after 10 gestational weeks. IFD was defined as fetal death after 20 weeks. The study was conducted in accordance with the Declaration of Helsinki, after approval by the Institutional Ethical Committee (protocol "MED-Mol" N. 62/INT/2021), and all patients signed a written informed consent.

All included patients had positivity for classical aPL (2). LLAC was detected according to international guidelines (37). aCL, aβ2GPI IgG and IgM antibodies and, when possible, also aPS/PT IgG and IgM were assessed by ELISA (QUANTA Lite ACA IgG and IgM, and β2-GPI IgG and IgM). All tests were conducted at the Department of Laboratory Medicine of our Institution, following validated procedures. INOVA Diagnostic Inc. provided aPS/PT IgG and IgM and were assessed on serum samples obtained at the first visit, immediately before or at the beginning of pregnancy. Medium aPL was defined as 20–40 U/ml, high aPL was defined as above 40 U/ml. For non-criteria a PL (aPS/PT), the cut off for defining positive aPL titer was 30 U/ml.

Pregnancy management

Gestational age was calculated as the time from the last menstrual cycle confirmed by ultrasound during the first trimester. If a strong discrepancy was noted between gestational and sonographic dating in a spontaneous pregnancy, the latter was used to date the pregnancy. At delivery, data regarding fetal and neonatal growth was collected. Preterm birth was defined as delivery occurring below 37 gestational weeks. APO were defined as: (a) fetal death occurring >10 weeks of gestation not explainable by chromosomal abnormalities, anatomical malformations, or congenital infections; (b) neonatal death occurring before hospital discharge due to complications of prematurity and/or placental insufficiency; (c) preterm birth occurring <37 weeks due to placental insufficiency, gestational hypertension, or (d) preeclampsia during gestation or puerperium (38). Ultrasonography was performed at 12 GW, 20 GW, 32 GW, 36 GW, and when fetal and/or maternal conditions required it. Every pregnancy was carefully monitored for the onset of arterial hypertension and/or preeclampsia (defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy as a *de novo* rise in systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg in the second half of pregnancy, and proteinuria ≥300 mg/24 h). IUGR was defined according to the World Health Organization classification as a child with weight at delivery <10th growth centile compared to the standard weight for sex and gestational age of 34 GW. Clinical Doppler ultrasound data (Pulsatility Index) were also collected during ultrasonography examination.

All patients during the enrolled pregnancies were treated with LDA (100 mg) from preconception and prophylactic LMWH (4,000 U daily) from the first US scan. LMWH was added according to EULAR recommendations (30). In patients with previous PE and/or DVT therapeutic dosage of LMWH were administrated. HCQ was added in APS secondary to SLE and/or in APS refractory to standard therapy (5, 31, 32, 39).

Placental histology

During the latter part of our recruitment process (2017–2023), after delivery, placentas underwent specific and not routine histological analyses aimed at assessing the main placental lesions described in APS (27). This approach enabled us to correlate histological findings with the clinical characteristics of the patients and pregnancies outcomes. Placentas were collected after cesarean birth or vaginal delivery and immediately fixed in 4%-neutral buffered formalin. All placentas were examined macroscopically and microscopically. Formalin-fixed placental weight and the percentage of macroscopic lesions on their surface were determined. Subsequently, two samples of the umbilical cord, fetal and placental membranes, and at least two samples of macroscopically normal placental tissue were taken from a central part of a placental cotyledon and from a peripheral area. Additional samples were also taken. Samples were processed and embedded in paraffin wax for histology.

Statistical analysis

Descriptive statistics were performed for all variables. Comparisons between groups were investigated using chi-square

test or student *T*-test for categorical and continuous variables respectively. Logistic regression was employed to determine whether HCQ treatment protected against placental lesions. Statistical significance was set at p values < 0.05.

Results

Patient characteristics

A total of 130 pregnancies in 96 patients with APS were included. Of these, 102 (78%) had primary APS while 28 (22%) had APS secondary to SLE. In twenty-four pregnancies (18%) was reported a previous thromboembolic diagnosis (i.e., venous thrombosis or pulmonary thromboembolism) and in 107 (82%) a history of APO. Only 8 patients did not have a previous pregnancy, while of the remaining 122 pregnancies, 68 (56%) had a previous liveborn baby. Overall, after being cared for in our Outpatient Clinic, 105 (81%) pregnancies culminated in an at-term delivery of a healthy child.

One hundred and ten (85%) pregnancies had a medium-high preconceptional aPL titer, while 20 (15%) had a low aPL titer. 29/130 pregnancies were conducted with triple aPL positivity. In these patients a statistical significant higher rate of previous thrombosis were reported (10 DVT/PE in 29 APS with triple aPL positivity vs. 14 DVT/PE in APS with single or double aPL positivity, $p = 0.045$). In 79 (61%) cases at least one previous early miscarriage was reported, 41 (32%) at least one late miscarriage and 18 (14%) IFD. The rate of successful anamnestic pregnancies was 56% (68/122). All patients and pregnancies characteristics are reported in Table 1.

During the index pregnancy, all patients received LDA 100 mg daily. In 109 (84%) pregnancies LMWH was added and in 26 (20%) were prescribed also hydroxychloroquine. 14/26 received HCQ for a SLE diagnosis and 12/26 received HCQ due to a previous refractory APS despite standard therapy with LDA and LMWH.

A total of 105 (81%) pregnancies gave birth to liveborn infants, 24 (18%) were diagnosed with early miscarriage and one patient had an IFD. Fetal/neonatal outcomes are detailed in Table 1.

TABLE 1 Clinical and laboratory characteristics of the cohort.

	Entire cohort	Patients whose placentas were analyzed	*P* value
Medical history	*N* = 130	*N* = 25	
Maternal age at conception (years)	33.58 ± 4.76	34.00 ± 5.06	0.23
Primary APS	102 (78)	19 (76)	0.78
aGAPSS (at conception)	9.41 ± 4.38	8.76 ± 4.17	0.24
>1 aPL positivity	54 (42)	15 (60)	0.09
Triple aPL positivity	29 (22)	8 (32)	0.29
High titer of aPL	110 (85)	19 (76)	0.30
Borderline aPL titer	20 (15)	6 (24)	0.72
aCL IgG/IgM	117 (90)	22 (88)	0.76
aβ2GPI IgG/IgM	52 (40)	12 (48)	0.40
LLAC and/or aPS/PT	29 (22)	7 (28)	0.53
TE-APS	24/130 (18)	1/25 (4)	0.07
Obstetrial medical history	***N* = 122**	***N* = 24**	
Previous newborn rate	68 (56)	12 (50)	0.61
≥2 miscarriages	65 (53)	16 (66)	0.23
≥3 miscarriages	37 (30)	9 (37)	0.49
IUGR/preeclampsia	7 (6)	4 (17)	0.06
Preterm birth	11 (9)	4 (16)	0.26
IFD	18 (15)	2 (8)	0.40
Therapy during pregnancy	***N* = 130**	***N* = 25**	
LDA + LMWH	110 (85)	25 (100)	0.13
HCQ	26 (20)	11 (44)	<0.05
Pregnancy characteristics	***N* = 130**	***N* = 25**	
Low complement level	13 (10)	3 (12)	0.76
Week of delivery	37.7 ± 2.8	37.4 ± 2.5	0.31
Liveborn infant	105 (81)	25 (100)	0.06
Birth weight (g)	2,953 ± 747	2,818 ± 593	0.20
Placental weight (g)	487 ± 152	441 ± 129	0.08
Miscarriage	24 (18)	0	NA
	***N* = 105 (newborn)**	***N* = 25 (newborn)**	
IUGR/preeclampsia	15 (14)	3 (12)	0.93
Preterm birth	16 (15)	4 (16)	0.92
IFD	1 (1)	0	NA

Continuous variables were expressed as mean ± SD, while categorical variables as absolute frequency (percentage).

TABLE 2 Placental histology.

Placental lesions	
Increased syncytial knots	17 (68%)
Decreased vasculosyncytial membranes	11 (44%)
Infarction	8 (32%)
Impaired spiral artery remodeling	3 (12%)
Decidual inflammation	2 (8%)
≥2 placental lesions	12 (48%)

Variables as absolute frequency (percentage).

Placental analyses

Twenty-five placentas of deliveries occurring during the last year of recruitment underwent specific placental analyses. Table 1 reports the clinical features, previous obstetrical history, and obstetrical outcomes of the pregnancies whose placentas were collected. No difference in patient and pregnancy characteristics was found between the entire cohort and the cohort of patients whose placentas were analyzed, suggesting that placental analyses were performed in a sample that was representative of the entire cohort (Table 1).

Mean placental weight was 441 ± 129 g. Frequencies of occurrence of each placental lesion among increased syncytial knots, decreased vasculosyncytial membranes, infarction, impaired spiral artery remodelling, and decidual inflammation were described in Table 2. Increased syncytial knots were the most frequent finding, being present in 17 (68%) placentas. Notably, 48% of placentas displayed more than two lesions.

The titer of aCL IgG was significantly higher in pregnancies whose placenta displayed syncytial knots (p 0.04, Table 3). In addition, a tendency towards higher aCL IgG titers were observed in pregnancies whose placentas had more than two

types of lesions (p 0.07, Table 3). No statistically significant differences were observed in the detection of more than two placental lesions between patients with primary APS and those with APS associated with SLE.

All patients with a history of thromboembolic event had placental infarction despite therapy (p 0.04, Table 3). Placental infarction was an independent predictor of placental weight at delivery independent of maternal age, its occurrence being associated with lower placental weight (p 0.04, Table 4). Also, a tendency was observed towards lower neonatal weight in the presence of placental infarction (p 0.08).

At logistic regression analyses, HCQ therapy during pregnancy did not predict any of the placental lesions analyses (Table 5). However, none of the pregnancies occurred in patients who received HCQ (11 out of 25) had decidual inflammation of the placenta, which was present in two of the 25 placentas analyzed (Table 5). Figure 1 depicts the main placental histological lesions.

Discussion

In this study of APS pregnant patients, we observed a high rate of successful pregnancy outcomes, largely due to specialized multidisciplinary care and specific therapeutic interventions. The low incidence of maternal complications and high live birth rates

TABLE 3 Pregnancies characteristics (n = 25) based on the presence or absence of placental lesion.

		≥2 histological placental lesions			Infarction			Decreased vasculosyncytial membranes			Increased syncytial knots		
	Overall	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*
Age at delivery (years)	34 (32–36)	36 (32.8–37.8)	33 (32–35)	0.11	35 (32–37)	32.5 (32–35.2)	0.48	32.5 (32–35.8)	36 (33.5–38.5)	0.19	35 (33–37.8)	34 (32–36)	0.28
BMI (kg/m^2)	21.4 (19.1–22.8)	22.1 (20.3–25.9)	20 (19.1–21.8)	0.23	21.4 (19.1–22.8)	21.1 (19.4–22.1)	0.93	21.1 (18.6–22.3)	21.8 (19.6–22.9)	0.48	22.3 (20.5–31.4)	20.8 (18.4–21.8)	0.08
Miscarriages	2 (1–3)	2.5 (1–3.2)	2 (1–2)	0.42	2 (1–4)	1.5 (1–2)	0.11	2 (1–2.8)	2 (1.5–4)	0.18	2 (1–2.5)	2 (1–3)	1
aGAPSS	8 (5–12)	8 (4.5–12.5)	8.5 (5.8–11.2)	0.59	8 (5–10.5)	10.5 (8.2–12)	0.22	10.5 (7.2–12.2)	5 (5–8)	0.19	8 (5–16)	8 (5–12)	0.8
aCL IgM titer	4.2 (0–28)	1.6 (0–28)	12.6 (1.5–26.2)	0.73	7.4 (0–28)	3.1 (1.5–10.4)	0.91	5.8 (1.2–33.8)	2 (0–25.3)	0.46	14 (0–28.8)	4.2 (0.8–23.1)	0.92
aCL IgG titer	7.4 (0–32)	0 (0–10.4)	25 (5.6–38.2)	0.07	0 (0–16.8)	32 (24–488)	0.15	13.6 (0–34.5)	0 (0–18)	0.44	0 (0–0)	16.8 (3.7–37.1)	0.04
B2GP1 IgM titer	1 (0–33.9)	1.5 (0–45)	0.5 (0–9.2)	0.51	1.5 (0–45)	0.5 (0–1)	0.32	0.6 (0–7.4)	1 (0–45)	0.76	22.5 (0–45.8)	1 (0–13.2)	0.71
β2GP1 IgG titer	6 (0–25.6)	21 (2.2–25.6)	5.7 (0–40)	0.80	5.4 (0–23)	50 (4.5–1,481)	0.39	14.8 (1.7–54.2)	6 (0–22)	0.59	21.5 (5.2–22.8)	5.4 (1.1–33.3)	0.95
aPS-PT IgM titer	29 (0–43.4)	29 (7.5–38)	20.4 (2.2–67.5)	0.94	25 (4.5–37.3)	53 (7.5–131.5)	0.50	36.7 (11.2–96)	10.7 (0–31)	0.13	31 (25–32.6)	22 (0–51.5)	0.73
aPS-PT IgG titer	5 (0–10)	5 (0–10)	3 (0–8.2)	0.94	6 (0–9.5)	0 (0–112.5)	0.84	0 (0–10.8)	6 (0–7.5)	0.94	7.5 (5–26)	0 (0–9.2)	0.22
APS secondary to SLE	6 (24)	2 (16.7)	4 (30.8)	0.72	4 (23.5)	2 (25)	1	3 (21.4)	3 (27.3)	1	2 (25)	4 (23.5)	1
≥2 miscarriages	16 (64)	8 (66.7)	8 (61.5)	1	12 (70.6)	4 (50)	0.58	8 (57.1)	8 (72.7)	0.7	5 (62.5)	11 (64.7)	1
LLAC	7 (28)	3 (25)	4 (30.8)	1	3 (17.6)	4 (50)	0.23	6 (42.9)	1 (9.1)	0.15	2 (25)	5 (29.4)	1
PE/DVT	3 (12)	0 (0)	3 (23.1)	0.25	0 (0)	3 (37.5)	0.04	3 (21.4)	0 (0)	0.31	1 (12.5)	2 (11.8)	1
≥1 miscarriage <10 gw	18 (72)	9 (75)	9 (69.2)	1	13 (76.5)	5 (62.5)	0.80	9 (64.3)	9 (81.8)	0.60	6 (75)	12 (70.6)	1
≥1 miscarriage >10 gw	8 (32)	5 (41.7)	3 (23.1)	0.57	6 (35.3)	2 (25)	0.95	5 (35.7)	3 (27.3)	0.98	3 (37.5)	5 (29.4)	1
IFD	2 (8)	1 (8.3)	1 (7.7)	1	1 (5.9)	1 (12.5)	1	1 (7.1)	1 (9.1)	1	2 (25)	0 (0)	0.17
Low complement	4 (16)	2 (16.7)	2 (15.4)	1	3 (17.6)	1 (12.5)	1	3 (21.4)	1 (9.1)	0.77	1 (12.5)	3 (17.6)	1
≥3 aPL positivities	8 (32)	4 (33.3)	4 (30.8)	1	4 (23.5)	4 (50)	0.38	7 (50)	1 (9.1)	0.08	2 (25)	6 (35.3)	0.95
≥2 aPL positivities	15 (60)	6 (50)	9 (69.2)	0.57	9 (52.9)	6 (75)	0.54	10 (71.4)	5 (45.5)	0.36	4 (50)	11 (64.7)	0.79

Continuous variables are expressed as median (interquartile range), while categorical variables as absolute count (percentage).

TABLE 4 Logistic and linear regression analyses predicting obstetrical outcomes.

	IUGR-preeclampsia/ preterm		GW at delivery		Neonatal weight at delivery		Placental weight	
	OR (95% CI)	*P*	Estimate (SE)	*P*	Estimate (SE)	*P*	Estimate (SE)	*P*
Infarction	5.72 (0.65–80.92)	0.13	−0.82 (1.08)	0.46	−419.24 (231.14)	0.08	−106.76 (49.01)	0.04
Decreased vasculosyncytial membranes	0.87 (0.08–7.08)	0.89	−0.17 (1.04)	0.86	184.81 (231.96)	0.43	59.46 (49.71)	0.24
Increased syncytial knots	0.37 (0.03–3.97)	0.40	1.47 (1.09)	0.19	5.12 (256.46)	0.98	−55.73 (54.64)	0.24
≥2 placental lesions	3.81 (0.42–84.64)	0.28	−0.18 (1.08)	0.87	−352.77 (231.05)	0.14	−110.22 (47.48)	0.03

TABLE 5 Logistic regression investigating whether HCQ treatment predicts each placental lesion, after adjusting for age at conception.

HCQ therapy	OR (CI 95%)	*P* value
Infarction	1.69 (0.27–12.87)	0.58
Decreased vasculosyncytial membranes	0.68 (0.11–3.86))	0.66
Increased syncytial knots	0.39 (0.04–2.63)	0.35
≥2 placental lesions	0.63 (0.11–3.66)	0.60

underscore the importance of specialized care in managing APS pregnancies. Standard therapy LDA and LMWH has been shown to significantly reduce the rates of miscarriages and late pregnancy complication (7, 30). Previous studies have consistently shown that standard therapy results in successful pregnancy outcomes in approximately 75%–80% of women with APS (40), a substantial improvement compared to their prior obstetric histories (10, 41, 42).

Despite these advancements, about 22% of APS women do not respond to conventional treatment with LDA and LMWH (40) and continue to experience adverse pregnancy events such as miscarriages, IFD, IUGR and preeclampsia. To address these refractory cases, additional treatments have been explored, including higher doses of LMWH, corticosteroids, intravenous immunoglobulin, plasma exchange, complement inhibitors, antitumor necrosis factor alpha, and HCQ (43).

HCQ has garnered particular interest due to its favorable safety profile during pregnancy, affordability, and ease of oral administration (31). Known for its anti-inflammatory and antithrombotic properties, HCQ is an old antimalarial drug that inhibits platelet aggregation and modulates immune responses (39, 44, 45).

Its potential role in reducing decidual inflammation—a key factor in adverse pregnancy outcomes—is especially significant. Several studies have shown that HCQ can improve obstetrical outcomes in APS patients (31, 39).

In our cohort, 25 placentas of pregnancies in APS patients underwent specific histological analysis. These pregnancies are representative of the typical population evaluated at our Clinic. Histological analysis of placentas from APS patients treated with HCQ revealed no instances of decidual inflammation, suggesting that HCQ may mitigate immune-mediated placental damage. This data need do be confirmed in a larger cohort of APS pregnant patients.

The presence of higher median titers of aCL IgG in placentas of pregnancies with two or more histological lesions and in those with increased syncytial knots, suggests that aCL IgG titers might serve as markers for predicting specific placental pathologies. Furthermore, all patients with a history of thromboembolic events exhibited placental infarction despite therapy, highlighting the ongoing risk of vascular complications in APS and the necessity of considering thromboembolic history in managing these cases.

Our findings align with previous literature indicating that placental lesions such as infarctions, impaired spiral artery remodeling, and decidual inflammation are common in APS and

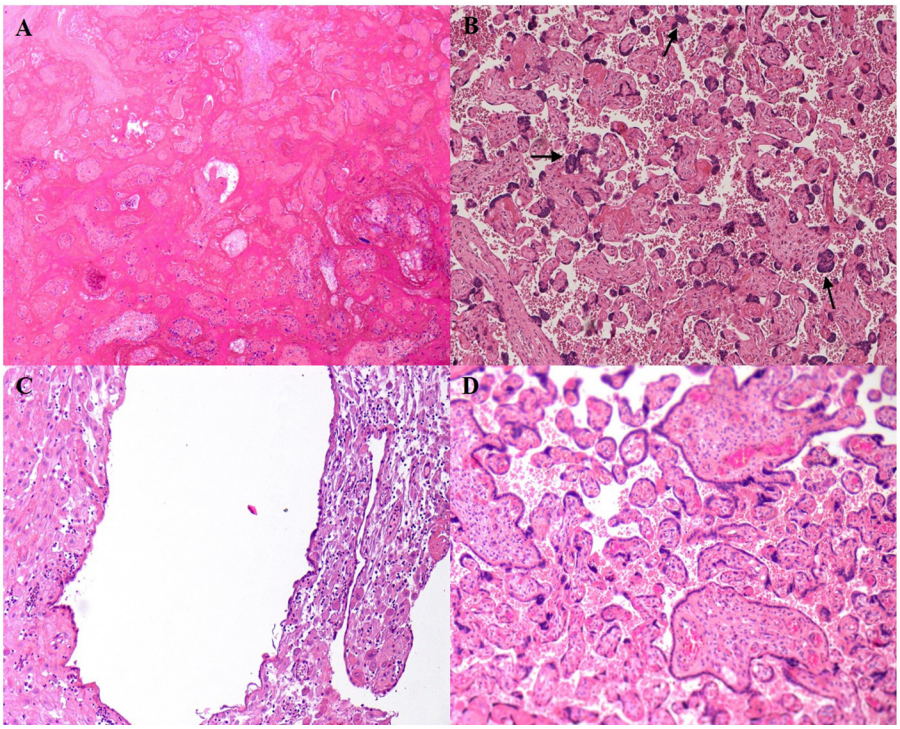

FIGURE 1
Placental histological lesions. **(A)** Placental infarction: the tissue is made up of ischemic "ghost" villi with mild inflammation in the lower-right part of the image. **(B)** Syncitial knots (arrows). **(C)** Deciduitis: lymphocytic inflammatory infiltrates in chorionic plate. **(D)** Normal placental tissue.

contribute to poor pregnancy outcomes (40). These lesions are believed to result from the direct binding of aPL to trophoblasts and other placental structures, leading to inflammation, thrombosis, and impaired placental development (10).

The role of HCQ in reducing these lesions is supported by its anti-inflammatory and antithrombotic effects. HCQ has been shown to decrease the binding of aPL to syncytiotrophoblasts and restore the expression of annexin A5, a protein that forms a protective anticoagulant shield on the placental surface (34, 44). Additionally, HCQ inhibits complement activation, which is crucial in mediating aPL-induced placental damage (36). These mechanisms suggest that HCQ may help preserve placental function and improve pregnancy outcomes in APS patients (46).

Given the known benefits of HCQ, initiating this treatment at the beginning of pregnancy with refractory APS, in addition to standard therapy, appears beneficial. The safety of HCQ during pregnancy is well-documented (45) and its efficacy in refractory APS is recognized (32). However, further studies with larger sample sizes are necessary to confirm these findings and elucidate the mechanisms by which HCQ may reduce placental lesions and improve pregnancy outcomes in APS patients.

Future research should focus on larger cohorts to better understand the impact of HCQ on placental pathology and adverse pregnancy outcomes. Detailed histopathological analyses and comprehensive clinical data will be critical for validating and expanding upon our findings. Understanding the specific pathways through which HCQ exerts its protective effects will help optimize treatment strategies for APS patients and potentially improve maternal and fetal outcomes.

In conclusion, our study underscores the significant impact of specialized multidisciplinary care in managing pregnancies affected by APS. The moderate-to-low levels of aPL titers observed in the 25 pregnancies may indicate a cohort with a potentially lower risk of adverse pregnancy outcomes (47). However, as the literature suggests (48), low aPL titers are more strongly associated with previous recurrent miscarriages. Our preliminary data also confirm the safety of using HCQ during pregnancy for both the mother and the fetus. Additionally, HCQ appears to offer extra benefits by reducing placental lesions. Larger studies are essential to fully understand the role of HCQ in improving pregnancy outcomes for APS patients, and the inclusion of detailed histopathological analyses and larger cohorts will be crucial for future research.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving humans were approved by Ospedale San Raffaele Ethical Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

VC: Writing – review & editing, Writing – original draft, Methodology, Formal Analysis, Data curation, Conceptualization. RD: Writing – review & editing, Writing – original draft, Formal Analysis, Data curation. GI: Writing – original draft, Data curation. SG: Writing – original draft, Methodology, Conceptualization. MP: Writing – original draft, Data curation. NT: Writing – original draft, Data curation. RL: Writing – original draft, Data curation, Conceptualization. FP: Writing – original draft, Data curation. MC: Writing – review & editing, Supervision, Data curation, Conceptualization. PC: Writing – review & editing, Supervision, Data curation, Conceptualization. P-RQ: Writing – review & editing, Supervision, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/flupu.2024.1459172/full#supplementary-material

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Challenging cases in rheumatic disease pregnancy: management perspectives from reproductive rheumatologists

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Pregnant women with rheumatic and musculoskeletal diseases (RMDs) have a higher risk of adverse pregnancy and perinatal outcomes compared to those without RMDs. Although evidence-based guidelines have been developed for the reproductive health care and management of these individuals, multiple areas of uncertainty exist around the diagnosis and treatment of pregnant patients with confirmed or suspected RMDs. We present a series of outpatient cases that address areas of uncertainty in the field of reproductive rheumatology. Expert opinions were elicited from rheumatologists who have expertise in the reproductive health of individuals with RMDs to build new understanding around diagnosis or treatment approaches. The cases focused on the interpretation of antiphospholipid antibodies in various clinical scenarios, diagnosis and management of nephrotic-range proteinuria during pregnancy, and the use of tumor necrosis factor inhibitors during pregnancy. Our objective was not to replace existing guidelines and classification criteria but rather to provide a range of expert opinions that rheumatologists might consider when tailoring treatment and care for patients, particularly in challenging situations with limited data.

KEYWORDS

reproductive health, women's health, lupus, antiphospholipid antibodies, treatment selection

Introduction

While many pregnant individuals with rheumatic and musculoskeletal diseases (RMDs) experience safe and healthy pregnancies, they have a higher risk of experiencing adverse pregnancy outcomes than individuals without RMDs, including preeclampsia, preterm birth, and maternal and fetal mortality (1). To enhance reproductive outcomes among individuals with RMDs and to standardize safe and effective treatment approaches during pregnancy, the European League Against Rheumatism (EULAR), the British Society for Rheumatology (BSR), and the American College of Rheumatology (ACR) have developed evidence-based guidelines for reproductive health (2–4). The ACR and EULAR have also codeveloped classification criteria for systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), both of which are associated with high risk of

pregnancy morbidity. APS in particular may co-occur with and complicate multiple RMDs (5, 6). In addition, the United States Preventive Services Task Force (USPSTF) has published a guideline for the use of low-dose aspirin to prevent preeclampsia in people with risk factors such as systemic lupus erythematosus and antiphospholipid syndrome (7).

However, guidelines and classification criteria do not—and cannot—address all of the real-world clinical scenarios that affect the care of pregnant individuals with RMDs. In clinical practice, rheumatologists may be confronted by challenging scenarios in the "gray zone" of management, without high-quality evidence or guidelines to support their medical decision-making. In this study, we present several cases from the outpatient clinical setting that address areas of uncertainty in the field of reproductive rheumatology. Rheumatologists with expertise in reproductive rheumatology served as clinical consultants and provided feedback about how they might approach the cases in their own clinical practices. Our objective was not to reach a consensus on the diagnosis or management of each case but to present different expert opinions that an outpatient rheumatologist might consider when developing their own diagnostic or treatment plans for pregnant patients with RMDs.

Materials and methods

The University of Pittsburgh Institutional Review Board deemed this study as exempt. Four rheumatologists were recruited via referral sampling based on their expertise in reproductive rheumatology, including clinical care and research related to pregnancy in the RMDs (LS, BB, CE, JZ); participation as co-investigators in the multi-site Maternal Autoimmune Disease Research Alliance (MADRA) Registry (LS, BB, CE, JZ); co-authorship of the 2020 ACR Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases, including service as guidelines chair (LS, BB); and dual certification in both pediatric and adult rheumatology (CE). These experts practice in academic rheumatology centers representing the northeast, southern, western, and midwestern regions of the United States.

Cases and clinical questions were informed by (1) the PI's (MBT) clinical practice, a specialized reproductive health and pregnancy-focused rheumatology clinic in the UPMC healthcare system (Pittsburgh, PA); (2) case presentations at the 12th International Conference on Reproduction, Pregnancy, and Rheumatic Diseases and other regional and national meetings; and (3) feedback from co-authors and other rheumatology colleagues. Cases were edited for simplicity and clarity, with the goal of highlighting one or two key topics of clinical uncertainty for discussion. The cases were circulated to the experts for review prior to a virtual group session. During the session, the PI presented each case as well as a series of clinical questions about diagnosis, management, or treatment. Twenty minutes of discussion were maximally allocated to each case. The session concluded with a discussion of other "gray zone" areas in the outpatient management of patients with RMDs. Cases, clinical questions, and expert opinions are presented in the Results section. Reference ranges are presented in Table 1.

Results

Case 1: does this pregnant patient have a high risk of obstetric antiphospholipid syndrome (OAPS) and require anticoagulation?

Interpreting antiphospholipid antibodies of unclear significance in a pregnant patient with recurrent pregnancy loss

CC: E.G. is a 25-year-old female, currently pregnant at 8 weeks of gestation (G3P020), who has a history of recurrent pregnancy loss. She has been healthy and is prescribed only a prenatal vitamin. She is referred to you because of abnormal labs ordered by her obstetrician:

- Antinuclear antibody (ANA): 1:80 speckled pattern
- Anticardiolipin antibody (aCL) IgM: 24.4 GPL

Obstetric History

- G3P0020

TABLE 1 Reference ranges for laboratory tests (5, 6, 18, 34).

Test	Reference ranges titer
Antinuclear antibody (ANA)	Normal: <1:80
Double-stranded DNA	Negative: <10 IU/ml
	Indeterminate 10–15 IU/ml
	Elevated: >15 IU/ml
Antiphosphatidylserine/prothrombin antibodies (aPS/PT) IgG/IgM/IgA	Low: <40 GPL
	Moderate: 40–79 GPL
	High: ≥80 GPL
Anticardiolipin antibodies IgG/IgM/IgA (aCL)	Low: <40 GPL
	Moderate: 40–79 GPL
	High: ≥80 GPL
Beta 2 glycoprotein I antibodies IgG, IgM, IgA (aβ2GPI)	Low: <40 GPL
	Moderate: 40–79 GPL
	High: ≥80 GPL
Lupus anticoagulant [prolonged partial thromboplastin time, dilute Russell's viper venom time (dRVVT), dRVVT 1:1 mixing study if dRVVT is prolonged, hexagonal phase confirmation]	Detected
	Not detected
	- PTT-LA screen ≤40 s
	- dRVVT screen ≤45 s
24-h urinary protein	Normal: 100 or 150 mg/day
Ro/La antibodies (SS-A, SS-B)	<1.9 AI
Smith/RNP antibodies	<1.9 AI
Scleroderma-70 antibodies	<1.0 AI
Jo-1 antibody	<1.0 AI
Rheumatoid factor (RF)	<14 IU/ml
Erythrocyte sedimentation rate (ESR)	0–20 mm/h
C-reactive panel (CRP)	<8.0 mg/L
Albumin	3.4–5.0 g/dl
Uric acid	2.5–6.2 mg/dl
Clinical disease activity index for rheumatoid arthritis (CDAI)	Remission: ≤2.8
	Low: >2.8–≤10
	Moderate: >10–≤22
	High: >22

- Three total pregnancies
  - 0 term births, 0 preterm births, 2 miscarriages, 0 living children
  - Currently pregnant
- Pregnancy 1: anembryonic pregnancy
- Pregnancy 2: intrauterine fetal demise at 25 weeks of gestation
  - Cause of death unknown
  - Pathology done outside the hospital: hemorrhagic findings were observed in the fetal lung, but no additional findings were reported.

Maternal Labs

- ANA 1:80 speckled
- Double-stranded (dsDNA) negative
- Extractable nuclear antigens negative
  - Ro/La (SSA/B)
  - Smith/RNP antibodies
  - SCL-70
  - JO-1
- Complements normal
- Antiphospholipid syndrome (APS) workup conducted 12 weeks apart:
  - aCL IgM 24.4 GPL, then 25.7 GPL 12 weeks later
    - aCL IgG and IgA negative
  - Lupus anticoagulant (LAC) negative
  - Beta-2-glycoprotein I (B2GPI) antibodies negative

Review of Systems and Physical Exam

- Feels well, but tearful and anxious about losing another pregnancy
- Vitals and physical exam normal

Update

- After the initial visit, a physician colleague orders antiphosphatidylserine antibodies with the following results, which remain positive on serial testing. You are asked to comment on these findings and the patient's risk of OAPS.
  - Antiphosphatiydylserine IgG > 150 GPL
  - Antiphosphatidylserine IgM > 150 GPL

In this case, the patient, who was pregnant, had previously experienced two recent and consecutive pregnancy losses—one pre-fetal loss (<10 weeks) and one fetal death at 25 weeks of gestation—without pathologic evidence of placental insufficiency. The patient had persistently positive anticardiolipin IgM antibodies at low titers. However, the patient also had high-titer antiphosphatidylserine (aPS) antibodies, which are not currently included in the classification criteria for antiphospholipid syndrome (APS). The clinical question was whether this patient should be treated for APS during the current pregnancy to prevent another pregnancy loss.

Antiphospholipid syndrome (APS) is an autoimmune condition that is associated with the presence of antiphospholipid antibodies [aPL, i.e., lupus anticoagulant (LAC) and/or anticardiolipin (aCL) or anti-beta-2-glycoprotein I IgG/IgM antibodies (aβ2GPI)] and evidence of thrombosis across the vasculature, including placental insufficiency and complement activation (8, 9). As detailed in the 2023 ACR/EULAR antiphospholipid syndrome (APS) classification criteria, pregnancy morbidity can be a manifestation of obstetric APS (OAPS), with clinical features that include pre-fetal death before 10 weeks of gestation, fetal death between 10 and 15 weeks or 16 and 34 weeks of gestation without preeclampsia or placental insufficiency, or preeclampsia or placental insufficiency with or without severe features and with or without fetal death (5). Points are assigned to each clinical and laboratory domain, and at least three points from each clinical or laboratory domain—with a total score of at least 6—are required to meet the classification criteria for APS.

Among the laboratory tests in the APS classification criteria, LAC explains most of the thrombotic risk attributed to antiphospholipid antibodies (10–13), and even if treated, people with positive vs. negative LAC have a 30% greater likelihood of adverse pregnancy outcomes (14). Other serologies associated with APS include positive aCL or anti-beta-2-glycoprotein I antibodies (5, 13). aCL or aβ2GPI IgG antibodies may be associated with pregnancy losses irrespective of titer; in contrast, the clinical significance of isolated aCL and aβ2GPI IgM isotypes is unclear and has not consistently been demonstrated to increase the risk of adverse pregnancy outcomes, particularly when in low or medium titers (<80 GPL) (14–17).

While not included in the current ACR/EULAR classification criteria for APS, antiphosphatidylserine/prothrombin (aPS/PT) antibodies are antiphospholipid antibodies that have been evaluated for potential significance in the diagnosis of APS (18). aPS/PT antibodies are detected by solid-phase assays and include antibodies to phosphatidylserine–prothrombin and prothrombin alone. These antibodies are less sensitive to anticoagulation and acute phase proteins than the LAC, although newer laboratory approaches can remove anticoagulants from plasma and increase the reliability of the LAC (19). Conflicting estimates of the sensitivity and specificity of aPS/PT antibodies have been reported in the literature, and while some prospective studies demonstrate an association of aPS/PT with thrombosis, small cohort sizes and restriction to single centers have limited the generalizability of findings (18, 19). In a communication from the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee, aPS/PT antibodies were not felt to provide additional value beyond LAC in the diagnosis of thrombotic APS but were felt to potentially add value to the diagnosis of thrombotic APS as compared to aCL and antibodies—particularly when present in high titers (19).

Antiphosphatidylserine/prothrombin antibodies may also add value to the diagnosis of OAPS. In a retrospective study of 653 controls and patients with OAPS and thrombotic APS, aPS/PT IgG or IgM were present in 40.5% and 32.1% of patients with OAPS, respectively (19). In regression analyses, OAPS was significantly associated with aPS/PT IgG and/or IgM, even after the addition of aCL IgG, aCL IgM, aβ2GPI IgG, or aβ2GPI IgM to models. However, when adjusting for the presence of LAC, the associations between aPS/PT IgG or IgM and OAPS became insignificant. These data suggested a possible added benefit of aPS/PT IgG and IgM in the workup of OAPS—particularly if LAC is negative. The associations of aPS/PT antibodies with APS were also evaluated in a study of Chinese patients with OAPS,

APS, and seronegative APS, many of whom had concomitant autoimmune or connective tissue diseases (20). The study reported that aPS/PT antibodies were detected in approximately 50% of seronegative APS patients, and over 90% of patients with LAC positivity also had positive aPS/PT IgG and IgM. In addition, aPS/PT IgG and IgM were strongly associated with fetal loss (OR 10.41, 95% CI: 5.47–21.63). These data cumulatively suggest that aPS/PT IgG and IgM antibodies are associated with adverse pregnancy outcomes; are correlated with LAC, which is the most robust test at present for diagnosing APS; and may potentially be useful in cases in which some index of suspicion for APS exists but other aPLs are negative or inconclusive.

Classification criteria are developed, in part, to standardize a patient population for research studies (21); thus, the ACR/EULAR criteria may have limited utility in the diagnosis of APS in real-world clinical practice. While many individuals affected by pregnancy loss may not meet the classification criteria for OAPS, other tests in the "gray zone" of diagnosis may help to support a clinical diagnosis of OAPS, which, if treated, can increase the likelihood of improved pregnancy outcomes (13). Recurrent and/or late-stage pregnancy losses can be devastating to patients and families, particularly when there is no clear etiology of fetal death. We sought to understand if and how reproductive rheumatologists used low-titer aCL and high-titer aPS/PT antibodies to evaluate a person with recurrent fetal loss.

Expert opinion

How would you approach determining if antiphospholipid syndrome had been a factor in the patient's two pregnancy losses?

Experts did not attribute the clinicopathologic finding of pulmonary hemorrhage on prior fetal autopsy to the patient's antiphospholipid antibodies. However, experts overwhelmingly felt that a review of the placental pathology of the prior pregnancy would have been important in determining if the antiphospholipid syndrome could have contributed to the earlier pregnancy losses. Experts recommended requesting a second histologic opinion from an academic-affiliated pathologist, as the pathologic review of the current case was limited. If no lesions characteristic of APS were observed in the placental pathology, experts felt that the likelihood of APS complicating the prior pregnancy was low despite the presence of high-titer aPS/PT antibodies.

Would you recommend anticoagulation to a pregnant person with recurrent, low-titer antiphospholipid antibodies and recurrent pregnancy loss?

Experts did not feel the patient's low-titer aCL IgM was a clinically significant finding and would not have recommend anticoagulation based on this individual result.

Do you check antiphosphatidylserine/prothrombin antibodies and in what contexts?

Most experts would consider checking aPS/PT antibodies in a patient with recurrent pregnancy losses with placental pathology suggestive of vascular insufficiency or thrombosis and who otherwise had negative lupus anticoagulant and subthreshold negative aCL and aβ2GPI. One expert routinely checked for antichromatin antibody levels and aPS/PT antibodies among patients whom they assessed for connective tissue disease and recurrent pregnancy losses. However, other experts rarely tested for aPS/PT antibodies as part of their approach for determining the etiology of pregnancy loss, unless clinical suspicion for APS was already high.

How would you treat this patient?

All experts would recommend low-dose aspirin (LDASA) at 12 weeks of gestation for primary prevention of preeclampsia for this patient with recurrent pregnancy loss and high-titer aPS/PT antibodies. Most experts did not feel that this patient required low-molecular-weight heparin (LMWH) based on her serologic profile and in the absence of compelling evidence of placental insufficiency. However, given the patient's devastating prior pregnancy outcomes, two experts felt that prophylactic-dose LMWH could have been considered and recommended a shared decision-making conversation with the patient to discuss the potential risks and benefits of treatment. Experts would not have recommended anticoagulation if the patient had high-titer aPS/PT antibodies without a history of recurrent fetal losses or other clinical evidence of APS.

Case 2: did this person have obstetric antiphospholipid syndrome and require anticoagulation in a future pregnancy?

Treatment decisions for a patient with positive antiphospholipid antibodies and a history of abnormal placental pathology who is planning for a future pregnancy

CC: D.C. is a 39-year-old, non-pregnant (G1P1) female, referred by her obstetrician for pregnancy planning. She was diagnosed with undifferentiated connective tissue disease (UCTD) by another rheumatologist due to sicca, fatigue, myalgias, arthralgias, and the following labs:

- ANA 1:1,280 speckled pattern; aβ2GPI antibody IgM, 59.7 GPL; aCL IgM, 25.8 GPL
- Negative or normal extractable nuclear antigens, rheumatoid factor (RF), complements, serum protein electrophoresis (SPEP), kappa lambda light chains, complete blood count (CBC), complete metabolic pattern (CMP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
- Normal eye exam (negative Schirmer/dry eye testing with ophthalmologist)
- Deferred minor salivary gland biopsy, sudomotor testing
- Multiple medication intolerances, could not tolerate brand or generic hydroxychloroquine

Obstetric History

- G1P1001
- 1 term birth, 0 preterm births, 0 abortions, 1 living child delivered 1 year ago
- Prior pregnancy: Healthy term pregnancy. Spontaneous vaginal delivery at 38 weeks

- Birthweight (21st growth percentile), normal APGAR. The child is healthy.
- Pathology: Obtained as the placenta appeared small in size. Features of maternal malperfusion were observed, with a hypoplastic placenta in the <3rd percentile of size, hypermature chronic villi, increased syncytial knots, delayed maturation, and involving up to 20% of villi examined. Narrow inserting three-vessel umbilical cord. No thrombi or infarcts were observed.

Maternal Labs

- ANA 1:1,280 speckled
- dsDNA negative
- Extractable nuclear antigens negative
  - Ro/La (SSA/B)
  - Smith/RNP
  - SCL-70
  - JO-1
- CBC, CMP, complements, RF, ESR, CRP, SPEP negative or normal
- Anti-beta-2-glycoprotein I (aβ2GPI) IgM 60.0 GPL on two occasions 12 weeks apart
  - aβ2GPI IgG, IgA negative
- Anticardiolipin (ACL) IgM 26.0 GPL on two occasions 12 weeks apart
  - ACL IgG and IgA negative on two occasions 12 weeks apart
- Lupus anticoagulant (LAC) negative on two occasions 12 weeks apart

Review of Systems and Physical Exam

- Multiple complaints on review of systems, including dysesthesias, fatigue, cognitive dysfunction, arthralgias, myalgias, hair shedding, and migraines
- Vitals and physical exam normal. Sensitive to light touch throughout the exam.

Update

- Another clinician rechecks antiphospholipid antibodies. Anti-beta-2-glycoprotein I and anticardiolipin antibodies are now negative. Testing was done in the same laboratory network but at a different laboratory than the prior testing. LAC remains negative.

In this "gray zone" case, the patient had a presumed diagnosis of undifferentiated connective tissue disease (UCTD) and was planning for a future pregnancy in the context of a prior term pregnancy with normal-weight neonate and placental findings suggestive of malperfusion or insufficiency. The patient also tested positive for moderate-titer aβ2GPI IgM antibodies and low-titer aCL IgM antibodies on two of three occasions.

UCTD is a condition in which a person has symptoms and/or laboratory tests that are suggestive of but do not meet the threshold for diagnosis of a specific connective tissue disease (CTD) such as systemic lupus erythematosus (SLE) or Sjogren's disease (22). UCTD may be associated with abnormal serologic findings, and in one review, 10%–24.8% of individuals with UCTDs have aPLs (23). Up to 30% of patients with UCTD, over time, will develop a systemic CTD, including diseases such as systemic lupus erythematosus, which has the potential to worsen during pregnancy (24).

As described in Case 1, placental insufficiency is included as a clinical domain in the 2023 ACR/EULAR antiphospholipid syndrome classification criteria and defined as estimated fetal weight of less than the 10th percentile for gestational age or postnatal birth weight less than the 10th percentile for gestational age in the absence of genetic conditions or fetal–neonatal syndromes associated with growth restriction. In addition, one or more of the following features are required: (1) fetal hypoxemia: abnormal or non-reassuring fetal surveillance tests or abnormal Doppler flow velocimetry waveform analysis; (2) severe intrauterine fetal growth restriction, defined as estimated fetal or postnatal birth weight of <3rd percentile for gestational age; (3) oligohydramnios; (4) maternal vascular malperfusion on placental histology: placental thrombosis/infarction, inadequate remodeling of the uterine spiral arteries, decreased vascular synctitial membranes, increased syncytial knots, or decidual inflammation.

Not all placental lesions are specific for APS. As indicated in the ACR/EULAR APS criteria, maternal vascular malperfusion on placental histology or small placenta size is insufficiently specific to add to the classification criteria for APS. Up to 50% of all healthy pregnancies demonstrate some evidence of vascular malperfusion, with increased incidence in the general population among pregnant people of advanced maternal age (age equal to or greater than 35, such as this patient) and/or who have obesity (25, 26).

EULAR recommends preconception or first-trimester use of LDASA for asymptomatic aPL carriers, people with SLE without prior thrombotic APS or OAPS, and females with OAPS history irrespective of pregnancy status (27). Among pregnant individuals with positive aPLs, the ACR Reproductive Health Guideline conditionally recommends treatment with LDASA starting in the first trimester if no prior thromboembolism or obstetric APS but does not advocate for the use of anticoagulation (2). UCTD alone is not an indication for anticoagulation during pregnancy, although an SLE diagnosis warrants treatment with LDASA starting around 12–16 weeks for preeclampsia risk reduction (2, 7, 28).

In contrast, the ACR Reproductive Health Guideline does advocate for treatment with prophylactic-dose LMWH and LDASA among people with obstetric APS and treatment with therapeutic-dose LMWH or unfractionated heparin (UFH) and LDASA for thrombotic APS (2). LMWH and UFH are associated with relatively few health risks to the pregnant person who requires anticoagulation and do not cross the placenta (29). UFH is associated with fewer bleeding episodes, a longer half-life, lower risk of heparin-induced thrombocytopenia, and less loss of bone mineral density than fractionated heparin. Enoxaparin, a type of LMWH, is associated with lower bleeding rates than full-strength aspirin, and bleeding rates are similar between enoxaparin users and untreated controls (30, 31).

In this case, while the patient had a prior healthy pregnancy outcome, OAPS was considered given positive antiphospholipid antibodies on two occasions and abnormal placental findings. However, subsequent antiphospholipid testing was negative. We sought to understand how experts would make decisions

around the patient's diagnosis and need for anticoagulation for a future pregnancy.

Expert opinion

How would you characterize this person's risk for adverse pregnancy outcome based on their possible UCTD diagnosis?

Most of the experts felt that a diagnosis of UCTD could provide more support for a diagnosis of APS; however, they felt that this patient's symptoms could also have been explained by fibromyalgia or centralized pain syndrome. Experts felt that the diagnostic testing for Sjogren's disease was incomplete. While the patient's ophthalmologic testing had not demonstrated dry eye, two experts advocated for minor salivary gland biopsy. One expert felt that if a diagnosis of Sjogren's disease was established, the addition of therapeutic-dose hydroxychloroquine could have been used to enhance pregnancy outcomes and perhaps provide a weak antithrombotic benefit to the patient given her positive aPLs. Other experts felt less confident that pregnant patients with Sjogren's disease benefitted from hydroxychloroquine during pregnancy, unless they had high-titer Ro or La antibodies; hydroxychloroquine has been suggested to reduce the incidence of congenital heart block as part of the neonatal lupus syndrome (2, 32). Experts would not have been more likely to provide anticoagulation to this patient even if Sjogren's disease were diagnosed, although several experts felt more confident that the aPLs could be clinically significant in that context.

Did this patient have obstetric APS in her first pregnancy?

Given the limited associations between aCL and aβ2GPI IgMs and adverse obstetric outcomes, experts felt that placental features of the prior pregnancy would be important in assessing the possibility of OAPS in this patient and guiding future treatment decisions. As placentas with evidence of malperfusion or hypoplasia are fairly common, even among healthy pregnancies, the pathology was not clearly suggestive of APS; however, several experts suggested that fetal growth restriction or small for gestational age birthweight (defined as birthweight <10th percentile for gestational age (33)) during the prior pregnancy would have strengthened their recommendations for anticoagulation during a subsequent pregnancy.

How would you treat this patient in a future pregnancy?

Given the positive aPLs on two of three occasions and non-specific evidence of placental malperfusion in the G1 pregnancy, all experts felt that LDASA was indicated in a subsequent pregnancy. The experts all agreed that the patient did not require anticoagulation while she was not pregnant. However, in the context of persistently elevated aPLs, experts felt that LMWH and LDASA could be appropriate treatments during a subsequent pregnancy, particularly if she was found to have a CTD with the completion of the diagnostic workup.

However, in the presence of the positive ANA, fibromyalgia, and variably elevated aPLs without objective evidence of a specific CTD —the current presentation of the patient— treatment recommendations varied between experts. Several experts did not feel that the combination of LMWH and LDASA was indicated for a subsequent pregnancy, whereas other experts felt that patient preference could guide the decision-making and anticoagulation would be reasonable if desired by the patient. Experts mentioned that other consultants, including hematologists and obstetrician-gynecologists, could also help the patient ascertain the risks and benefits of treatment or non-treatment. In this case, the patient had poor tolerance of conventional medications and generally preferred a non-pharmacologic approach.

How do you make treatment decisions when a person has had contradictory tests for antiphospholipid antibodies?

In this case, aβ2GPI and aCL antibodies were positive on two separate occasions 12 weeks apart but were negative when tested several weeks later. The negative test diminished most of the experts' interest in treating the patient with LMWH in a subsequent pregnancy. Experts described a common challenge in the diagnosis of APS as the requirement of serial testing over at least a 12-week period, and if conducted in different laboratories, could yield variable and contradictory results due to differences in the calibrations and standards across assays. Most experts therefore advised patients to receive repeat aPL testing in the same clinical laboratory if possible.

Case 3: does this pregnant patient have lupus nephritis?

Making treatment decisions for a pregnant patient with nephrotic-range proteinuria without a renal biopsy

CC: R.L. is a 32-year-old female, currently pregnant at 18 weeks of gestation (G3P1011), who was incidentally found by her obstetrician to have proteinuria of around 3 g per day. Nephrology was consulted and ordered low-dose aspirin; however, they refused renal biopsy as they felt she was a high risk for poor postprocedural outcomes. Rheumatology was consulted to evaluate for lupus nephritis due to the following results:

- ANA 1:1,280–1:5,120 titers with cytoplasmic patterns
- Negative renal ultrasound with dopplers, no thrombus observed

Obstetric History

- G3P1011
- 1 term birth, 0 preterm births, 1 miscarriage, 1 living child
- Prior pregnancy loss: 25 weeks of gestation in 2018. Placental/fetal pathology not obtained.
- Subsequent pregnancy was complicated by gestational hypertension, but the infant was full term and normal weight. The child is healthy.
- Currently pregnant at 18 weeks of gestation.

Maternal Labs

- ANA 1:1,280–5,120 cytoplasmic pattern
- dsDNA 14 IU/ml (intermediate finding) on two occasions, negative (<10) 6 weeks later
- Remaining extractable nuclear antigens negative

  - Ro/La (SSA/B)
  - Smith/RNP
  - SCL-70
- Complements normal
- CBC normal
- Creatinine 0.4–0.6 mg/dl
- Albumin 3.0 mg/dl
- Uric acid 4.9 mg/dl
- Anti-phospholipase A2 receptor (PLA2R) antibody negative
- Antiphospholipid syndrome workup:
  - Lupus anticoagulant positive on 2 occasions
  - Anticardiolipin IgM GPL 22.5, negative on 1 occasion
  - Anti-beta-2-glycoprotein I IgM GPL 24.2, negative on 1 occasion
- Urine white blood cells and red blood cells within normal limits

Review of Systems and Physical Exam

- Feels well, no complaints
- Blood pressure 101/71, other vitals and physical exam normal with exception of body mass index of 50

Update

Proteinuria

– 16 weeks of gestation: 3,017 mg (24 h urine collection)
– 19 weeks of gestation: 2,890 mg (24 h urine collection))
– 22 weeks of gestation: 6,030 mg (24 h urine collection)

In this case, the pregnant patient, who was healthy except for an elevated BMI of 45, was incidentally found to have nephrotic-range proteinuria; subsequent workup revealed high-titer ANA, weakly positive double-stranded DNA antibodies, and persistently positive lupus anticoagulant. She had a prior pregnancy that ended in fetal death at 25 weeks of gestation, with no placental pathology or fetal autopsy performed. The clinical question was if the nephrotic-range proteinuria in this case was indicative of lupus nephritis (LN); at the patient's institution, renal biopsy was considered too high-risk to perform given her stage of pregnancy and elevated BMI.

Mild proteinuria is common in normal pregnancy and can rise from a healthy pre-pregnancy range of 0–150 mg/dl prior to 300 mg/dl during pregnancy; the highest levels of urinary protein are generally observed in the second and third trimesters. Urinary protein levels greater than 300 mg/day increase suspicion of glomerular disease (34). Preeclampsia, a hypertensive disorder of pregnancy that is associated with sustained blood pressure elevation, is a common cause of nephrotic-range proteinuria after 20 weeks of gestation (35). At any stage of pregnancy, however, proteinuria can also be secondary to focal segmental glomerulosclerosis, minimal change disease, diabetes, APS nephropathy, or systemic lupus erythematosus, among other rare diagnoses such as amyloidosis (34).

The gold standard for urinary protein quantification is the 24 h urine collection, although the protein/creatinine ratio is highly correlated with 24 h protein quantification. Nephrotic-range proteinuria includes proteinuria of greater or equal to 3.5 g/day over 24 h, hypoalbuminemia (less than 3.5 g/dl), and peripheral edema. Serum albumin concentration also decreases during pregnancy; thus some studies suggest using different cutoffs for hypoalbuminemia depending on trimester, i.e., albumin <3.1 g/dl in the first trimester, <2.6 g/dl in the second trimester, and <2.3 g/dl in the third trimester (34, 36). Hypoalbuminemia is particularly important when considering risks associated with nephrotic syndrome, such as venous thromboembolism, which can occur among up to 40% of patients with nephrotic syndrome—particularly those with membranous glomerulonephritis. Thrombotic risk appears to increase with decreasing serum albumin, particularly in individuals with serum albumin less than 2.5 g/dl (37).

Renal biopsy is a critical part of the workup of nephrotic-range proteinuria, particularly in cases with diagnostic uncertainty (38). Renal biopsy is overall a safe procedure but can be associated with microhematuria and perirenal hematoma, and the incidence of postprocedural complications ranges from 2% to 6.7% (38). Generally, renal biopsy can be safely performed on the pregnant patient prior to 25 weeks of gestation (39); however, gestational limits around renal biopsies may differ across institutions, particularly those with limited expertise in the procedure.

In this case, the rheumatology service was asked to comment on the possibility of SLE and lupus nephritis. New SLE can arise during pregnancy. Several small studies suggest that new-onset SLE tends to occur during the first and second trimesters, and LN is more commonly seen in new-onset SLE during pregnancy than SLE diagnosed in non-pregnant individuals (40). However, SLE can be challenging to diagnose during pregnancy. Complements C3 and C4 rise by 10%–50% during normal pregnancy, which can mask hypocomplementemia secondary to immune activation; erythrocyte sedimentation rate can increase by 30%–70%; mild dilutional anemia and thrombocytopenia in the range of 100–150,000/microliter are common, and mild proteinuria can be physiologic (41). Certain subtypes of LN can also be difficult to diagnose—for example, membranous glomerulonephritis is associated with nephrotic-range proteinuria, but many patients lack the systemic symptoms associated with SLE (e.g., fevers, rash, serositis, inflammatory arthritis), and renal pathology is often needed to confirm the diagnosis (42, 43).

Pregnant individuals with SLE have at least a twofold higher risk of preeclampsia than other pregnant individuals (35)—particularly individuals who have lupus nephritis—however, LN and preeclampsia can be difficult to differentiate from each other. Preeclampsia and LN can also present concurrently in the same patient—leading to greater complexity in diagnosis (41, 44). Both can be associated with hypertension, progressive renal insufficiency, hemolysis, and thrombocytopenia (41). However, as preeclampsia is a manifestation of placental insufficiency, urgent delivery of the fetus may be indicated, whereas in LN, delivery is not an approach to treatment. Uric acid levels can help to differentiate LN from preeclampsia; uric acid levels may be high in preeclampsia but are generally normal in LN (44). The ratio of the serum soluble fms-like tyrosine kinase 1 (sFLt-1) to placental growth factor (PlGF), which is not yet widely used in the United States, is an angiogenic marker that has the potential to differentiate between preeclampsia—in which the ratio is elevated—and other etiologies of hypertensive disorders of pregnancy or LN (45).

The limited availability of effective and pregnancy-compatible treatments can undermine LN management for the pregnant patient (2). As described in the ACR and EULAR guidelines for reproductive health management, mycophenolate mofetil or mycophenolic acid and cyclophosphamide—the first-line drugs for severe LN—are known teratogens (cyclophosphamide can be used in later stages of pregnancy for severe and organ-threatening disease) (2). LN treatments that are compatible with pregnancy have some limitations. High-dose steroids, typically recommended for severe LN, are immunosuppressive and, at doses of prednisone higher than 20 mg daily, can enter the fetal circulation, which may potentially lead to neonatal adrenal suppression. Hydroxychloroquine, while safe at all stages of pregnancy and not immunosuppressive, is an ineffective monotherapy for LN. Azathioprine is a second-line treatment for LN that is safe for the fetus at all stages of pregnancy but, in inflammatory bowel disease, has been associated with a rare but elevated risk of intrahepatic cholestasis of pregnancy that might warrant its discontinuation if bile acid and liver function tests are elevated; this complication has rarely been reported in patients with SLE, but requires future study (46). Calcineurin inhibitors can be used to reduce proteinuria, but their efficacy as stand-alone agents in LN or in SLE is unclear based on a paucity of data in diverse cohorts (6). Rituximab may be used in organ-threatening renal disease, but administration in the second or third trimester has been associated with reversible but months-long CD19+ B-cell depletion in the neonate (2, 47). Thus, advancing treatment in cases of diagnostic uncertainty given the potential side effects of treatment and unclear clinical outcomes can be challenging during pregnancy.

Experts were asked about how they might manage the asymptomatic pregnant patient with high-titer ANA, low or indeterminate-range dsDNA, positive lupus anticoagulant, and nephrotic-range proteinuria without renal pathology.

Expert opinion

What are your leading differential diagnoses?

Experts' leading differential diagnoses included lupus nephritis, membranous glomerulonephritis, focal segmental glomerulosclerosis (obesity as a risk factor), ANCA vasculitis, and thrombotic microangiopathy related to APS. Experts felt it would be helpful to ascertain if the patient had proteinuria prior to the pregnancy; if not, they felt that this might increase suspicion of new-onset lupus nephritis and APS nephropathy, both of which can develop in pregnancy. Gestational cutoffs for renal biopsy varied across experts' institutions, and across institutions, experts reported variable levels of enthusiasm among renal and interventional colleagues in facilitating renal biopsies. Overall, experts felt this case would be difficult to diagnose accurately without a renal tissue sample; however, they felt that the management of nephrotic-range proteinuria was straightforward.

How did laboratory and ultrasound testing assist with refining the differential diagnosis without biopsy, and would any additional labs be helpful?

One expert recommended checking anti-chromatin antibody level, and if positive, would consider treating as LN. PLA2R antibody, which is highly specific for idiopathic membranous nephropathy, was negative in this case, which was helpful in reducing suspicion of membranous nephropathy. Ultrasound with Doppler was normal in this case, reducing suspicion of renal vein thrombosis from APS. C1q antibodies, if orderable at the institution, could have increased suspicion for proliferative lupus nephritis.

Would you recommend any treatment to this person?

All experts recommended starting prednisone (corticosteroid) at doses between 20 mg and 60 mg daily for nephrotic-range proteinuria; one expert indicated that they would provide pulse dose steroids over a 3 day period and then transition to calcineurin inhibitors. Most experts advocated for the consideration of calcineurin inhibitors to treat proteinuria. One expert recommended checking for antichromatin antibody; if positive, they would treat with azathioprine for presumed lupus nephritis. Experts felt that hydroxychloroquine was a medication with a low risk of side effects and could be added to the treatment as lupus nephritis was on the differential. Azathioprine was considered reasonable if the suspicion of lupus nephritis was moderate or high, but experts were unsure that it would be indicated for the other diagnostic considerations.

One expert indicated that most people with proteinuria over three grams daily should receive anticoagulation with low-molecular-weight during pregnancy, no matter the etiology, due to increased thrombotic risk. Another expert indicated that if a patient's albumin level was less than 2 mg/dl in the context of nephrotic-range proteinuria, they recommended anticoagulation during pregnancy. These recommendations are consistent with published guidance (48). The patient's persistently positive lupus anticoagulant augmented experts' strong recommendation for treatment-dose anticoagulation during pregnancy.

Case 4: should this pregnant patient with rheumatoid arthritis switch from adalimumab to certolizumab pegol for safety reasons?

Treatment decision-making around tumor necrosis factor inhibitors during pregnancy

CC: M.R. is a 25-year-old female, currently pregnant at 16 weeks of gestation (G1P0), with a history of seropositive rheumatoid arthritis (RA). She is prescribed adalimumab. Her sister-in-law, an internist, reviewed the ACR Reproductive Health Guideline and recommended switching to certolizumab from adalimumab based on the recommendations. M.R. seeks your opinion.

Past Medical History

- Diagnosed at age 20 with severe synovitis of the MCPs, PIPs, and wrists. No erosions on radiographs. She is otherwise healthy.
- Treatment history: Failed methotrexate, leflunomide. Transitioned to adalimumab 2 years ago.
- Current medications: Adalimumab taken subcutaneously every 2 weeks. Prenatal vitamin.

Review of Systems and Physical Exam

- Pain of 2 out of 10 in severity, which is stable. Forty-five minutes of morning stiffness, also stable.
- Swelling/tenderness of right metacarpophalangeal joints 2 and 3.
    - Clinical disease activity index (CDAI): 6 (low disease activity)

In this real-world case, the pregnant patient has seropositive rheumatoid arthritis (RA) treated with adalimumab. She is experiencing low but persistent disease activity. She is questioning if she should be switched to certolizumab for safety reasons now that she is pregnant.

RA disease activity improves for 40%–90% of patients during pregnancy; however, only a minority of patients experience remission, approximately 20% of women experience severe or worsening RA over pregnancy, and treatment is often needed through pregnancy to preserve functional status (49, 50). Pregnancy-compatible treatments for RA include hydroxychloroquine, sulfasalazine, prednisone, and tumor necrosis factor inhibitors (TNFi) (2). NSAIDs can be safely used before 20 weeks of gestation as per the Food and Drug Administration guidelines (51). In addition, while RA symptoms may improve during pregnancy, RA patients still have a higher risk of preeclampsia, preterm growth, and fetal growth restriction than pregnant individuals without RA (52). Treatment during pregnancy may facilitate better pregnancy outcomes among patients with RA; for example, in one study, treatment with TNFi during pregnancy was associated with increased birth weight of infants born to patients with well-controlled RA (53).

TNFi are immunosuppressive medications that increase the risk of infection in adult patients (54). TNFi can be detected in umbilical cord blood, increasing concern for neonatal immunosuppression and potential risk of infection (55). Multiple studies have not found significant associations between fetal exposure to TNFi and serious neonatal infections (56, 57). However, to reduce potential infection risk, the ACR Reproductive Health Guideline conditionally recommends discontinuing the TNFis adalimumab, infliximab, golimumab, and etanercept in the third trimester of pregnancy or several half-lives prior to delivery, as these medications pass into the fetal circulation in the late stages of pregnancy (2).

In contrast to other TNFi, certolizumab pegol, a PEGylated TNFi, has very minimal or no active placental transfer because of its molecular structure; thus, the developing fetus is unlikely to be exposed to the treatment during pregnancy (58, 59). Thus, certolizumab does not need to be discontinued during any stage of pregnancy to reduce the risk of neonatal immunosuppression (2). Given a case of fatal disseminated tuberculosis in a neonate who was exposed to infliximab during pregnancy and received Bacillus Calmette-Guerin (BCG) vaccination at 3 months of age, certolizumab is favored above the other TNFis in countries in which TB is endemic and/or BCG vaccination is administered within 6 months of age (60).

Because the studies of certolizumab pegol in pregnancy and lactation are arguably more robust than other pregnancy studies of TNFi, and because it does not pass into the placental circulation, certolizumab is strongly recommended in the ACR Reproductive Health Guideline (2). In contrast, adalimumab, infliximab, golimumab, and etanercept—other TNFis that are not PEGylated and can cross into the placental circulation—are conditionally recommended during pregnancy (2).

Given these recommendations, some clinicians choose to switch RA patients using adalimumab, infliximab, golimumab, and etanercept to certolizumab during pregnancy—as was recommended in this case—to optimize safety in the pregnant patient. However, no available data assess the pregnancy and perinatal outcomes of people who switch to certolizumab from another TNFi. The risk of RA flare during a switch in treatment could augment the risk of adverse pregnancy and perinatal outcomes, including maternal pain and loss of function. Insurance coverage may also be a barrier to switching TNFi to certolizumab. We queried experts about how they might advise a pregnant patient with mildly persistent RA about TNFi treatment selection and management.

Expert opinion

Would you advise switching this patient from adalimumab to certolizumab from a safety perspective?

All experts would continue adalimumab in this patient with persistent RA without switching to certolizumab during pregnancy. Experts felt that TNFis were safe during all stages of pregnancy from the perspective of fetal development. Experts felt the risk of disease flare is moderate when switching TNFis during pregnancy, which could increase the risk of preterm birth and preeclampsia. Experts felt that ideally, patient-clinician discussions around treatment should occur prior to pregnancy in the case of a planned or anticipated pregnancy; switching treatments during pregnancy was not ideal given the risk of precipitating a disease flare.

How would you advise the patient to manage her treatment in the third trimester if she continues to have disease activity?

All experts agreed that the patient could safely continue adalimumab during all trimesters of pregnancy and should hold the adalimumab at 32 weeks of gestation *only if* the disease was well-controlled. For patients with persistent RA, most experts felt that patients could either stop the adalimumab at 36 weeks of gestation or, if the disease continued to be persistent and limiting, would continue through all stages of pregnancy. All experts felt that the poor outcomes associated with active RA were of greater concern than the theoretical risk of neonatal immunosuppression. Experts indicated that publications about the infection risk in neonates who have been exposed to a TNFi in the third trimester have been reassuring all experts felt that if the patient had ongoing disease activity, the patient should be treated in the third trimester and beyond without treatment modification.

Experts varied in their recommendations if a theoretical cesarean operation was planned for this patient with persistent RA activity, given the potential for maternal infection or impaired wound healing. One expert recommended continuing the patient's adalimumab until 36 weeks of gestation if a planned surgery (e.g., cesarean section) was scheduled at around 37 or 38 weeks. Most

experts felt that missing one or two doses of TNFi would not significantly affect the patient's disease activity, and she could resume her treatment immediately after delivery. Two experts also indicated that most patients at their institutions were advised by obstetrician-gynecologists to hold their TNFi for 3 weeks prior to delivery.

Summary

While available guidelines and classification criteria have supported effective diagnosis and treatment of autoimmune conditions during pregnancy, we highlight several of the many "gray zones" that exist in the management of pregnant patients with RMD. Pregnant patients who are severely ill may receive aggressive treatments that are in the grey zone, and such management might be easily justified in the service of preserving maternal and/or fetal life. However, we felt that there is a significant benefit in highlighting outpatient cases with diagnostic or treatment uncertainty, as rheumatologists are more likely to encounter and care for patients in non-critical clinical scenarios.

Some rheumatologists might feel uncomfortable advancing treatments for pregnant people who appear clinically or medically stable. If so, this would be understandable; pregnant individuals have been largely excluded from randomized clinical trials of treatments due to ethical concerns, so clinicians have been left in the position of having to manage the pregnancies of people with known or suspected autoimmune diseases with limited and sometimes poor-quality evidence to support their decision-making. Rheumatologists may also feel concerned about exposing pregnant patients to medications that have side effects or have questionable safety during pregnancy. The inability at some institutions to advance diagnostic testing during pregnancy, such as renal biopsy (e.g., Case 3), may further undermine some rheumatologists' comfort level in advancing treatments that may immunosuppress the patient and/or are associated with side effects. Ultimately, some rheumatologists may feel that advancing treatments for the pregnant patient in the context of diagnostic uncertainty and without critical illness, might undermine their oath of *primum non nocere—to first do no harm*.

However, non-action may also not serve the patient and cause harm. An important ethical consideration is that treatment during pregnancy may be necessary to prevent organ failure or severe maternal morbidity or mortality, even when limited diagnostic data are available to guide medical decision-making. In addition, failure to treat or to advance care may lead to adverse outcomes that eventually threaten maternal and fetal health, even if the pregnant patient appears immediately stable.

Robust data are urgently needed to inform medical decision-making for pregnant individuals with RMDs. In addition, shared medical decision-making between patient and physician is essential in developing a treatment plan in the gray zone of management. In this context, clinicians share the potential risks and benefits of various approaches and provide their interpretation of a clinical case. Some patients may feel inclined toward treatment whereas others may not. In these cases, the clinician's ideal role is to facilitate the patients' goals-concordant care if clinically reasonable and support them throughout their pregnancy experience along with other medical specialists (61). Even in the case of an adverse outcome, the patient will have participated in the treatment decisions and had the opportunity to express their goals and preferences for care.

In addition to the four cases discussed herein, experts felt that discussion of other "gray zone" areas in outpatient management should involve international reproductive rheumatology colleagues to ascertain regional differences in approaches, share experiential knowledge, and build new understanding and shared strategies in treating patients in the grey zone of management. The International Conference on Reproductive, Pregnancy, and Rheumatic Diseases (also known as Rheumapreg) provides one important venue for international collaborations. Our reproductive rheumatology experts were particularly interested in future discussions about placental pathology interpretation continuation or discontinuation of IL-1, IL-6, IL-17 and IL12/23 inhibitors in spondyloarthritis, belimumab usage during lupus pregnancy, and consideration of low-dose aspirin for all pregnancies of patients with RMDs.

Experts also advocated for multidisciplinary collaborations when assessing gray zone cases. For example, placental pathologies that might seem alarming to the rheumatologist might be less concerning to a maternal–fetal medicine specialist; conversely, serologic profiles that appear alarming to non-rheumatologists might be less concerning to the rheumatologist (e.g., an isolated positive ANA). Hematologists might expand a thrombotic workup to include genetic thrombophilia tests, some of which may be fairly unfamiliar to rheumatologists but may inform assessment of thrombotic risk and anticoagulation decisions. Multidisciplinary collaboration can help to more accurately evaluate clinical scenarios as well as the risks and benefits of different diagnostic and treatment approaches. In addition, a cohesive message shared by the multidisciplinary team may help to provide confidence and reassurance to the pregnant individual and family.

The expert opinions shared herein are not meant to be interpreted as evidence-based guidelines or criteria and might differ from the perspectives and opinions of other experts in the field. However, this manuscript serves to provide rheumatologists with points of consideration as they approach the outpatient care of pregnant patients. Ultimately, shared decision-making and multidisciplinary collaboration between the pregnant patient and the clinician team are essential for advancing person-centered, preference-concordant health care in the reproductive rheumatology context.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the University of Pittsburgh Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article because we adapted case reports to have different patient initials, ages, lab values, and other clinical features. These cases are not recognizable, but the principles in management are emphasized. In addition, we created two *de novo* cases that were informed by questions provided at meetings.

Author contributions

IM: Conceptualization, Investigation, Project administration, Writing – original draft, Writing – review & editing. BB: Writing – original draft, Writing – review & editing. CE: Writing – original draft, Writing – review & editing. LS: Writing – original draft, Writing – review & editing. JZ: Writing – original draft, Writing – review & editing. MB: Conceptualization, Data curation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ataxic sensory neuronopathy with isolated anti-Ro/SS-A antibody during pregnancy: a case report of adverse outcomes

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We present the rare case of a 33-year-old pregnant woman who developed severe ataxic sensory neuronopathy associated with isolated anti-Ro/SS-A antibodies without other features of Sjögren's syndrome. Her symptoms, which began with numbness and paresthesia, progressed to severe ataxia and sensory impairment, complicated by preeclampsia and intrauterine fetal death. Despite treatment with intravenous immunoglobulin, azathioprine, and steroids, she remains disabled. This case raises awareness for anti-Ro/SS-A antibodies in pregnant women and underscores the importance of early intervention and a multidisciplinary approach to prevent severe neurological disability.

KEYWORDS

sensory neuronopathy, pregnancy, anti-Ro/SS-A antibodies, Sjogren's syndrome, fetal death

Introduction

Sensory neuronopathies (SNNs), or ganglionopathies, are rare, specific subgroups of neuropathies characterized by primary and selective degeneration of sensory neurons in the root dorsal ganglia (DRG), leading to severe ataxia and asymmetric, non-length-dependent sensory symptoms responsible for significant disability (1, 2). In contrast to classical polyneuropathies, they are more frequently associated with immune-related disease, neoplastic origins, and toxic agents (3).

The most dysimmune-related diseases associated with SNNs are Sjogren's syndrome, coeliac disease, and autoimmune hepatitis (4). In Sjogren's syndrome, SNNs can precede the onset of sicca symptoms and be the first presentation. In such cases, the presence of anti Ro/SS-A antibodies can be a highly valuable diagnosis.

During pregnancy, anti-Ro/SSA and anti-La/SSB antibodies have been associated with a risk for neonatal lupus and congenital heart block (CHB). But there were no adverse maternal outcomes (5).

Here, we report a rare case of a pregnant African young woman who experienced severe onset ataxic sensory neuronopathy associated with isolated anti Ro/SS-A antibodies without other features of Sjogren's syndrome, leading to intrauterine fetal death, pre-eclampsia, and neurologic disability despite intravenous immunoglobulin, azathioprine, and steroid treatment.

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Case description

A 33-year-old African G2P0 woman, with a history of unexplained second-trimester pregnancy loss and a family history of undifferentiated connective tissue disease in her sister, presented at 20 weeks gestation with subacute numbness and paresthesia in her feet and palms. Three weeks later, she was admitted to the gynecology department for headaches, hypertension, and proteinuria. She was diagnosed with pre-eclampsia, complicated by intrauterine fetal death, on ultrasonography.

The neurologic problem was also noted and worsened with the onset of balance disturbances and acroataxia in the lower limbs, symptomatically treated with gabapentin. After managing the pre-eclampsia and fetal expulsion, she was referred to the neurology and internal medicine departments for further investigations.

The clinical exam revealed normal muscle strength using the Medical Research Council (MRC) scale, proprioceptive gait ataxia, pseudoathetotic movements of the fingers, a positive Romberg sign, and a generalized absence of deep tendon reflexes. The arms and legs exhibited hypoesthesia for touch, and all four limbs exhibited hypoesthesia for vibration and proprioception. There was no purpura, skin rash, Raynaud phenomenon, malar rash, arthralgia, arthritis, parotidomegaly, or adenomegaly. Electromyography showed normal nerve motor conduction, while sensory nerve conduction demonstrated an absence of sensory response and a negative H reflex consistent with sensory neuronopathy (Table 1).

Her inflammatory markers revealed an accelerated sedimentation rate of 50 mm in the first hour, C-reactive protein at 14 mg/L, and hypergammaglobulinemia at 18 g/L without monoclonal gammopathy at immunoelectrophoresis.

Initial workups for vitamins B6 and B12 showed normal results. Negative results were obtained for tests conducted on antinuclear antibody, anti–double-stranded DNA (dsDNA) antibodies, antiphospholipid lupus anticoagulant, anticardiolipin, Beta-2-glycoprotein 1, anti-neutrophil cytoplasmic antibody (ANCA), cryoglobulin, rheumatoid factor, and anti-citrullinated protein antibodies (ACPA). Complements C3 and C4 were within the normal range. In addition, the results of thyroid tests, celiac disease antibody tests, and serial neuronal antibody tests were all within normal.

Interestingly, anti-Ro/SS-A antibodies were positive at 86 U/ml. The patient denied having Sicca syndrome. Further investigation of salivary accessory gland histology was normal; Schirmer's test and ophthalmic exam were normal. A CT scan of the chest, abdomen, and pelvis revealed no adenopathy, pulmonary involvement, or tumoral lesions. Serological tests for HIV, HCV, and HBV were negative.

A diagnosis of autoimmune sensory neuronopathy (SNN) was considered probable based on the pattern of her neuropathy, with a Camdessanche's score >6.5 and the presence of anti-Ro/SS-A antibodies. She was initially treated with IV methylprednisolone (1 g/day for 3 days) with oral tapering. In the second week, due to lack of improvement, intravenous immunoglobulin at doses of 0.4 g/kg/day for 5 days was initiated, along with azathioprine 2 mg/kg/day (Figure 1). She noticed stabilization and mild improvement in sensory function, a decrease in numbness and paresthesia, and a partial return of deep tendon reflexes. The treatment was well tolerated, and the patient reported clinical improvement in her symptoms. However, she remained disabled at the 3-month follow-up with a modified Rankin Scale (mRS) score of 4.

TABLE 1 Sensory nerve conduction study.

Nerve	SNAP amplitude (μV)	SCV (m/s)
R sural nerve	NR (>10)	NR (>40)
L sural nerve	4	45
R superficial peroneal nerve	4 (>8)	38 (>40)
L superficial peroneal nerve	3	40
R median nerve	3 (>20)	50 (>45)
L median nerve	4	46
R ulnar nerve	NR (>20)	NP (>45)
L ulnar nerve	8	52
R radial nerve	NR (>18)	NR (>50)
L radial nerve	4	50

Discussion

This patient demonstrates a rare and challenging case of sensory neuronopathy onset in a pregnant woman with isolated anti-Ro/SS-A antibodies, emphasizing the importance of a thorough early workup for neuronopathy in pregnancy, prompt treatment of this rare and severe neuropathy subset, which is typically less responsive to classic treatments, and vigilant monitoring of pregnancy outcomes in the presence of anti-Ro/SS-A antibodies.

Sensory neuronopathies, also known as ganglionopathies, are a rare and specific subgroup of neuropathies characterized by degeneration of sensory neurons in the dorsal root ganglia (DRG); they impair both central and peripheral sensory pathways (1). The DRGs are particularly vulnerable to cytotoxic T cells because of their permeable blood-nerve barrier, leading to paraneoplastic sensory ganglionopathy when tumor antigens cross-react with sensory neurons (6). Similarly, Sjögren's syndrome and idiopathic cases are mediated by CD8 cytotoxic T cells (3, 6).

Compared to classical polyneuropathies, SNNs are more commonly associated with immune-related diseases, neoplastic origins, and toxic agents (1). SNNs autoimmune-related diseases include Sjögren's syndrome, coeliac disease, and autoimmune hepatitis (4, 7). Sjögren's syndrome is the most common autoimmune disease related to SNNs. It primarily affects exocrine glands through epithelial lymphoid infiltration, leading to ocular and oral dryness. However, one-third of patients have systemic extra-glandular manifestations, including pulmonary, renal, vascular, or neurologic involvement (8). Among these, neurological manifestations affect the peripheral nervous system in 20%–25% of patients (9); sensory axonal neuropathy and small fiber neuropathy are the most frequent; sensory neuronopathy is less frequent but the most severe form, affecting up to 5% and leading to major disability (10). SNNs can precede the onset of sicca symptoms, making diagnosis difficult. In such cases, the presence of focal sialadenitis with focus score ≥1

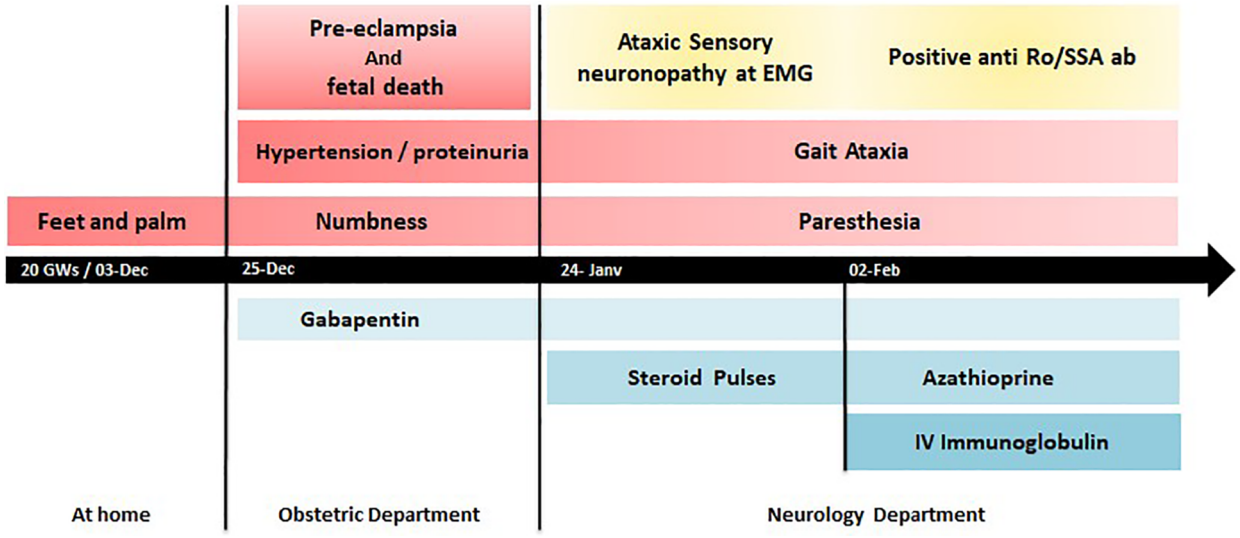

FIGURE 1
Timeline of symptom onset and therapeutic management of ataxic sensory neuronopathy.

focus/4 mm^2 of glandular tissue and anti-Ro/SS-A, anti-La/SS-B antibodies is highly valuable for diagnosis. Mostly found in systemic lupus (30%–40%) and Sjogren's syndrome (50%–90%), anti Ro/SS-A antibodies are also present in other autoimmune diseases (11).

Pregnancy may reveal preexisting autoimmune disorders or exacerbate symptoms in existing conditions such as lupus erythematosus. The presence of anti-Ro/SS-A antibodies raises concerns due to the potential adverse outcomes, especially in associated Sjögren's syndrome with systemic lupus erythematosus or antiphospholipid syndrome (12, 13).

This patient's neurological examination revealed prominent gait ataxia, pseudoathetotic movements of the fingers, positive Romberg sign, and generalized absence of deep tendon reflexes. Sensory examination showed hypoesthesia to touch, vibration, and proprioception in all four limbs, with no significant muscle weakness. These clinical signs were suggestive of the SNNs diagnosis, which was confirmed by primary sensory neuropathy on electromyography (EMG) with a Camdessanche's score of >6.5 points (14).

Laboratory investigations showed elevated inflammatory markers, including an accelerated sedimentation rate, elevated C-reactive protein, and hypergammaglobulinemia suggestive of dysimmunity. Despite extensive investigations for paraneoplastic syndrome, notably with negative CT imaging, serial onconeuronal antibody, vitamins, and coeliac antibody tests, only the anti Ro/SS-A antibodies were positive, with negative antinuclear antibodies in indirect immunofluorescence. Isolated anti-Ro/SS-A antibodies are mainly associated with Sjögren's syndrome and systemic lupus erythematosus. Salivary gland histology and Shirmer's test were normal, antinuclear antibody, anti-ENA and anti-dsDNA were negative. Despite the absence of classic Sjögren's features, this patient's positive SNNs-associated anti-Ro/SS-A antibodies indicate an autoimmune origin, possibly Sjögren's syndrome.

While primary Sjögren's syndrome is associated with a lower risk of obstetric complications compared to associated lupus or antiphospholipid syndrome, the presence of isolated anti-Ro/SS-A antibodies raises pregnancy risks for congenital complete atrioventricular block (13), especially in severe cases with non-glandular manifestations. Although anti-Ro/SS-A antibodies and primary Sjögren's syndrome do not usually increase the risk of pre-eclampsia (15), in our case, management of the pre-eclampsia and intrauterine fetal death complicated delayed explorations and treatment initiation. The risk of obstetric complications in the presence of isolated anti-Ro/SS-A antibodies should not be underestimated.

Several treatments have been tested on small groups of patients with autoimmune sensory neuropathies (SNNs), including steroids, intravenous immunoglobulin (IVIG), plasma exchange, azathioprine, rituximab, and cyclophosphamide (6, 16). These treatments have shown varied efficacy, with patients experiencing a 20% improvement and 12% stabilization in symptoms (16). A retrospective study of 13 people with SNNs connected to Sjögren's syndrome found that the best treatment was a mix of steroids and immunosuppressants, especially mycophenolate mofetil (MMF). However, intravenous immunoglobulins produced disappointing findings (17). Moreover, not all of these treatments are safe during pregnancy.

In our case, the delayed identification of anti-Ro/SS-A antibodies resulted in a delay in initiating steroid pulse therapy. The patient's clinical symptoms improved after receiving intravenous immunoglobulin and azathioprine, but she remains disabled. Cyclophosphamide was avoided due to the risk of infertility, and plasmapheresis was not available.

Currently, there is no consensus on treating SNNs with anti-Ro/SS-A antibodies in pregnancy due to a lack of high-quality evidence on the best treatment strategy. This highlights the crucial role of multidisciplinary team management, including obstetricians, neurologists, and rheumatologists, along with the shared decision-making process.

Conclusion

This case emphasizes the necessity of conducting anti-Ro/SS-A antibodies screening in individuals with neuropathy symptoms, rheumatic disease, a previous occurrence of fetal loss, intrauterine fetal death, or fetal heart block, regardless of the absence of classical signs of Sjögren's syndrome. Early diagnosis and aggressive treatment with immunomodulatory therapies can prevent irreversible neuronal damage and enhance outcomes for SNNs patients. Further trials and research are needed to understand the pathophysiological mechanisms and the best treatment strategy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RS: Investigation, Methodology, Writing – original draft, Writing – review & editing. ZF: Data curation, Investigation, Methodology, Writing – review & editing. SE: Investigation, Writing – review & editing. MB: Investigation, Methodology, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Low-dose aspirin in systemic lupus erythematosus pregnancy: impact on pregnancy outcomes and optimal management

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Systemic lupus erythematosus (SLE) presents unique challenges in pregnancy management due to the increased risk of pregnancy-related complications and potential for disease flare during pregnancy. In all SLE pregnancies, low-dose aspirin (LDA) is recommended to reduce the risk of preeclampsia, a significant pregnancy complication, despite limited evidence specifically targeting this population. This study aimed to evaluate the efficacy of LDA in improving pregnancy outcomes among patients with SLE and to explore the optimal dosage and timing of LDA administration. We conducted a retrospective single-center study including 75 pregnancies, the majority of which were planned except for three unplanned cases. Adverse pregnancy outcomes (APOs) were observed in 32 pregnancies (42.6%), with low birth weight being the most frequent ($n = 25$, 33.3%), followed by preeclampsia ($n = 16$, 21.3%). In our study with a limited sample size, no significant differences in APOs were found between the LDA-prescribed and non-prescribed groups. However, within the LDA prescribed group, earlier initiation before 6 weeks of gestation, was associated with significantly higher birth weights ($p = 0.01$) and lower rates of early onset preeclampsia ($p = 0.04$) compared to later administration. Additionally, a daily 100 mg dose was more beneficial than an 80 mg dose in improving birth weight ($p = 0.002$) and reducing the frequency of APOs ($p = 0.01$). Our study highlights the necessity of assessing individual risk when prescribing LDA in lupus pregnancies and the potential benefits of early initiation and optimal dosing of LDA in improving pregnancy outcomes.

KEYWORDS

pregnancy, adverse pregnancy outcome, low-dose aspirin, systemic lupus erythematosus, antiphospholipid antibody

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects females of childbearing age (1). Family planning is a crucial consideration for all individuals, and those with SLE should have access to the same reproductive options as the general population. However, pregnancy in patients with SLE requires special attention due to the increased risk of pregnancy-related complications, such as preeclampsia, preterm delivery, and other adverse pregnancy outcomes (APOs), as well as the risk of disease flare (2–4). Preeclampsia is a particularly significant concern in

pregnant patients with SLE, not only because of the higher risk relative to healthy individuals but also due to the difficulty in distinguishing it from flare of lupus nephritis, a manifestation of disease activity. The clinical features of these conditions can be very similar, yet they require distinct therapeutic approaches (5). Previous studies have shown that patients with lupus have a higher risk for preeclampsia, complicating in 9%–23% of pregnancies (2, 6). Additionally, the presence of active lupus nephritis further increases the risk of developing preeclampsia (7).

Given the significance of preeclampsia in pregnant patients with SLE, the prescription of low-dose aspirin (LDA) as a preventive measure is conditionally recommended for all patients with SLE, as well as for all antiphospholipid antibody (aPL) positive patients, according to the 2020 American College of Rheumatology (ACR) guideline for the management of reproductive health in rheumatic and musculoskeletal diseases (RMD) (8). This prophylactic measure is recommended to commence in the first trimester with 81 or 100 mg of daily LDA. However, the recommendation acknowledges that the quality of evidence is "very low" especially among patients with negative aPL tests, as there are no prospective studies specifically evaluating the impact of LDA therapy on pregnancy risks in patients with SLE, and the existing data are all observational (8–10). Thus, it remains uncertain whether all patients with lupus are at an elevated risk for pregnancy complications, particularly those without established risk factors such as concomitant lupus nephritis, aPL positivity, and active serological and clinical disease status (4, 11). In line with this, the European Congress of Rheumatology (EULAR) recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with SLE and/or antiphospholipid syndrome (APS) advocate the use of LDA in patients with SLE who are at higher risk for preeclampsia, including those with nephritis or positive aPL (12). Adding to the inconclusive evidence on the LDA use on lupus, with slight variations among clinical guidelines, the optimal dosage and initiation timing of LDA remains unclear.

In this study, we aim to address 2 key points that arise from the limited existing evidence. First, we investigate whether LDA impacts pregnancy outcomes in patients with lupus, considering the presence of aPL positivity. Second, we seek to determine the optimal dose and initiation timing of LDA in pregnancies in patients with SLE.

Methods

This is a retrospective single center study conducted at University of Tsukuba Hospital. We included 75 pregnancies in patients with SLE who were followed at the hospital from January 2017 to January 2022. All patients fulfilled the 2019 EULAR/ACR classification criteria for SLE (13). All the clinical, serological, and pregnancy outcome data were collected from the medical records. Diagnosis of APS followed the revised Sapporo classification criteria (14) and retrospectively confirmed fulfilling 2023 ACR/EULAR classification criteria (15). Antiphospholipid antibody positivity was defined in accordance with the 2023 classification criteria, using ELISA by LSI Medience, Japan. Non-criteria antiphospholipid antibody positivity was defined as either low-titer positivity observed in one or multiple examinations or as a non-persistent single positivity (detected only once across multiple examinations conducted at least 12 weeks apart). To maintain consistency and reliability, the aPL profile was determined exclusively on the tests conducted in our hospital.

APOs included early spontaneous abortion before the 10th week of gestation, preeclampsia (early-onset: before 34 weeks of gestation, late-onset: at or after 34 weeks of gestation), preterm delivery before 37 weeks of gestation, low birth weight (less than 2,500 g), and intrauterine fetal death after 12 weeks of gestation. We analyzed pregnancy outcomes considering 2 groups: those with APS diagnosis and criteria aPL positivity, and those without, to minimize the potential interference of aPL positivity on pregnancy outcomes, given the significant impact of aPL positivity and APS diagnosis on pregnancy outcomes in patients with lupus (4, 16–18).

Statistical analysis was conducted using GraphPad Prism version 10.0 (GraphPad Software, San Diego, CA, USA). Continuous variables were described using median and interquartile range (IQR), while categorical variables were presented as frequencies and percentages. For comparing continuous variables between 2 groups, Mann-Whitney *U*-test was employed, due to the small sample size. Categorical variables were analyzed using Fisher's Exact test.

Approval for this study was obtained from the Clinical Research Ethics Review Committee, University of Tsukuba Hospital (approval number: H29-154). With the approval of the Clinical Research Ethics Review Committee at the University of Tsukuba Hospital, the requirement for written informed consent was waived using the opt-out method on the website (https://tsukubarheumatology.jp/), due to the retrospective and observational design of the study, which utilized only clinical data obtained through daily clinical practice.

Results

Characteristics of the study population

The study included 75 pregnancies from 57 Japanese women. The characteristics of the study population are shown in Table 1. The median age at conception was 32 years (IQR 29–35.5), and 10 pregnancies (13.3%) were supported by assisted reproduction therapy clinics. Among these pregnancies, 20 (26.6%) involved prior miscarriages, 8 (10.6%) had a history of preeclampsia, and 27 (36.0%) were primipara. Comorbidity risk factors included hypertension in 7 pregnancies (9.3%), obesity in 11 (14.6%), and smoking in 14 pregnancies (18.6%). In our study population, underweight (BMI <18.5) was more frequently observed than obesity. Serological activity of lupus was assessed by measuring the median anti-DNA antibody titer, which was 7 IU/ml, (IQR 3.5–16.9), the C3 level, which was 84 mg/dl (IQR 70.5–93.5), the C4 level, which was 14.65 mg/dl (IQR 11–18.25), and the CH50

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TABLE 1 Baseline characteristics at conception.

		All (n = 75)	No LDA (n = 44)	LDA (n = 31)	P-value
Age at pregnancy, years		32 (29–35.5)	32 (29–35.2)	33 (30–35.5)	0.49
Assisted reproduction techniques, n (%)		10 (13.3%)	7 (15.9%)	3 (9.6%)	0.50
Prior miscarriage, n (%)		20 (26.6%)	9 (20.4%)	11 (35.4%)	0.18
Unplanned pregnancy, n (%)		3 (4.0%)	1 (2.2%)	2 (6.4%)	0.56
Primipara, n (%)		27 (36.0%)	17 (38.6%)	10 (32.2%)	0.63
Hypertension		7 (9.3%)	5 (11.3%)	2 (6.4%)	0.69
Obesity (BMI 25≦)		11 (14.6%)	6 (13.6%)	5 (16.1%)	0.75
Underweight (BMI <18.5)		18 (24%)	12 (27.2%)	6 (19.3%)	0.58
History of preeclampsia		8 (10.6%)	4 (9.0%)	4 (12.9%)	0.71
Smoking		14 (18.6%)	9 (20.4%)	5 (16.1%)	0.76
Markers of disease activity					
Anti-DNA antibody (IU/ml)		7 (3.5–16.9)	6.5 (3–11.6)	7 (4–24.2)	0.37
High antibody titer, n (%)		38 (50.6%)	12 (27.2%)	16 (51.6%)	0.05
C3 (mg/dl)		84 (70.5–93.5)	86 (72–100.2)	83 (70–90)	0.17
Low C3 titer, n (%)		13 (17.3%)	8 (18.1%)	5 (16.1%)	0.99
C4 (mg/dl)		14.6 (11–18.2)	15 (11–19)	13 (10.5–17)	0.23
Low C4 titer, n (%)		22 (29.3%)	10 (22.7%)	12 (38.7%)	0.19
CH50 (U/ml)		49.2 (39.8–58.1)	53.1 (42.2–59.5)	49.2 (38.1–53.2)	0.20
Low CH50 titer, n (%)		9 (12%)	4 (9.0%)	5 (16.1%)	0.47
Platelet count ($\times 10^3$/μl)		22.7 (17.3–26.0)	23.0 (17.1–26.3)	21.1 (17.9–25.5)	0.49
Lupus nephritis, n (%)		17 (22.6%)	9 (20.4%)	8 (25.8%)	0.58
UPCR (g/gCr)		0.07 (0.05–0.11)	0.07 (0.05–0.10)	0.08 (0.07–0.11)	0.24
SLEDAI-2K score		2 (2–4)	2 (0.75–4)	2 (2–4.5)	0.42
LLDAS achievement		24 (32%)	17 (38.6%)	7 (22.5%)	0.20
APS and aPL positivity					
APS diagnosis, n (%)		9 (12%)	1 (2.2%)	8 (25.8%)	0.002**
Obstetric complication, n (%)		1 (1.3%)	0 (0%)	1 (3.2%)	0.41
Thrombosis, n (%)		8 (10.6%)	1 (2.2%)	7 (22.5%)	0.007**
Criteria aPL positivity, n (%)		12 (16%)	1 (2.2%)	11 (35.4%)	0.0001***
Non-criteria aPL positivity, n (%)		15 (20%)	4 (9.0%)	11 (35.4%)	0.007**
Medication					
IS	Glucocorticoids, n (%)	69 (92%)	40 (90.9%)	29 (93.5%)	0.99
	Prednisolone dose (mg/day)	10 (5–10)	8 (5–10)	10 (6.5–10)	0.19
	Hydroxychloroquine, n (%)	13 (17.3%)	9 (20.4%)	4 (12.9%)	0.28
	Tacrolimus, n (%)	25 (33.3%)	14 (31.8%)	11 (35.4%)	0.80
	Azathioprine, n (%)	3 (4.0%)	3 (6.8%)	0 (0%)	0.26
Biologics	Belimumab, n (%)	3 (4%)	3 (6.8%)	0 (0%)	0.26
Numbers of IS used					
0		43 (58.6%)	27 (61.3%)	16 (51.6%)	0.47
1		16 (21.3%)	8 (18.1%)	8 (25.8%)	0.56
2		12 (16%)	7 (15.9%)	5 (16.1%)	0.99
3		4 (4%)	2 (4.5%)	2 (6.4%)	0.99

P-values for the comparison between LDA-prescribed pregnancies and non-prescribed pregnancies are shown. Fisher's exact test was used for categorical variables, and Mann-Whitney U-test was used for continuous variables. UPCR, urine protein/creatinine ratio; IS, immunosuppressive therapy.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

****$P < 0.0001$.

level, which was 49.2 U/ml (39.85–58.17). The median platelet count was 22.7×10^3/μl (IQR 17.3–26). SLEDAI-2 K score, reflecting overall disease activity, was 2 (IQR 2–4). These results reflect that most patients conceived under well-controlled disease. However, despite stable disease activity according to SLEDAI-2 K scores and serological findings, 68% of the pregnancies were not in LLDAS remission status, primarily due to the prescribed dose of prednisolone. Most of the pregnancies were planned, except for three, necessitating treatment change when the physician became aware that the patients were pregnant. In one of these cases, the patient was exposed to mycophenolate mofetil, which was discontinued immediately upon the physician's recognition of the pregnancy. A history of lupus nephritis was present in 17 pregnancies (16%), with a median urine protein to creatinine ratio of 0.07 g/gCr (IQR 0.05–0.11). At conception, most cases of lupus nephritis were in remission, with urine protein levels below

0.5 g/gCr, except for two cases of active nephritis, both of which were in unplanned pregnancies.

Regarding medication use, glucocorticoids were prescribed in 69 pregnancies (92.0%), with a median dosage of 10 mg/day (IQR 5–10) as prednisolone equivalent. A total of 62.6% of the pregnancies were treated with more than 7.5 mg/day, which accounted for 92.1% of the cases for not achieving LLDAS status. Hydroxychloroquine was used in 13 pregnancies (17.3%). Other immunosuppressants used included tacrolimus in 25 pregnancies (33.3%), azathioprine in 3 pregnancies (4.0%), and belimumab in 3 pregnancies (4.0%). Immunosuppressants, in addition to glucocorticoids, were used in 31 pregnancies (41.3%), with 1 immunosuppressant used in 16 pregnancies (21.3%), 2 in 12 pregnancies (16%), and 3 in 3 pregnancies (4%). All immunosuppressants were initiated before conception.

APS diagnosis was made in 9 pregnancies (12%), with previous thrombotic events in 8 patients (10.6%), and obstetric complications in 1 patient (1.3%). Among the 8 patients with a history of thrombotic events, 4 pregnancies were managed with anticoagulation during pregnancy. Criteria aPL positivity was observed in 12 pregnancies (16%), while non-criteria aPL (not persistent or low titer) was observed in 15 pregnancies (20%). For the determination of the non-criteria aPL profile, one case was examined nine times, two cases were examined eight times, three cases were examined six times, two cases were examined five times, one case was examined four times, two cases were examined three times, tree cases were examined twice, and one case was examined only once. Among aPL-positive pregnancies, triple aPL positivity was significantly more frequent in pregnancies with criteria-positive aPL, while single aPL positivity was more common in those with non-criteria aPL (Supplementary Table S1). Additionally, LAC positivity was significantly higher in pregnancies with criteria-positive aPL compared to those with non-criteria aPL ($p = 0.0004$, Supplementary Table S1).

LDA as a prophylactic treatment during pregnancies was prescribed in 31 pregnancies (41.3%), with a dose of 81 mg in 14 pregnancies (18.6%), and 100 mg in 17 pregnancies (22.6%). Among the pregnancies prescribed with LDA, it was initiated before 6 weeks of gestation in 19 pregnancies (61.2%), with the majority (16 pregnancies) starting even before conceiving. Later initiation timing varied between 10 and 16 weeks of gestation. No significant differences were observed between the LDA and non-LDA prescribed groups in terms of markers of SLE activity, frequency of renal disease, or medication use. However, there was a significant difference in the prevalence of aPL positivity and APS diagnosis. Among the LDA prescribed group, there was a significantly higher prevalence of APS diagnosis and positivity for both criteria and non-criteria aPLs (APS: 1/44, 2.2% vs. 8/31, 25.8%, $p = 0.002$; criteria aPL: 1/44, 2.2% vs. 11/31, 35.4%, $p = 0.0001$; non-criteria aPL: 4/44, 9.0% vs. 11/31, 35.4%, $p = 0.007$), particularly in those with a history of thrombotic events (1/44, 2.2% vs. 7/31, 22.5%, $p = 0.007$). Interestingly, when analyzing the basic characteristics at conception, excluding pregnancies with lupus nephritis, which is one of the main factors related to APOs (4), no significant difference was observed in the prevalence of non-criteria aPL positivity between the LDA-prescribed and non-prescribed groups (Supplementary Table S2). Notable variability exists in both dosage and timing of LDA initiation, particularly among those commenced after 6 weeks of gestation.

Pregnancy outcome

Overall, APOs occurred in 32 pregnancies (42.6% of all pregnancies) as shown in Table 2. The most common APO observed was low birth weight, occurring in 25 pregnancies (33.3%), followed by preeclampsia in 16 pregnancies (21.3%), and preterm delivery in 13 pregnancies (17.3%). Disease flare of SLE, necessitating treatment changes, occurred in 8 pregnancies (10.6%). Among these disease flares, the recurrence of cutaneous symptoms was the most frequent manifestation, observed in 4 cases, followed by nephritis in 2 cases, worsening serological markers in 1 case, and onset of thrombotic microangiopathy (TMA) in 1 case. There was no significant difference in the frequency of total APOs (18/44, 40.9% vs. 14/31, 45.1%, $p = 0.81$) or observed disease flare between pregnancies that were not prescribed LDA and those that were. When analyzing the use of LDA in relation to APOs across all patients, including those with APS or of the aPL positive criteria, no significant differences in pregnancy outcomes related to LDA use were found. To account for the potential effect of APS/aPL positivity, we analyzed the total APOs after excluding 15 of those patients. Again, no significant difference was found between the LDA-prescribed and non-prescribed patients (17/42, 40.4% vs. 8/18, 44.4%, $p = 0.77$). While APS diagnosis and criteria aPL are associated with APOs, non-criteria aPL, especially low titer aPL, is also reported to be related to APOs (19). Accordingly, we compared APOs between patients with APS or criteria aPL positivity, those with non-criteria aPL positivity, and those with no aPL positivity (Supplementary Table S3). The results indicated that spontaneous abortion prior to 10 weeks was significantly higher in pregnancies with non-criteria aPL positivity ($p = 0.03$). In summary, our study, with its small sample size and primarily planned pregnancies, did not reveal a significant difference in APOs among all patients with lupus, including those with APS/criteria aPL, nor among patients with lupus without APS/criteria aPL between the LDA-prescribed and non-prescribed groups. Additionally, a more detailed analysis of the aPL profile suggested a potential contribution of non-criteria aPL to early spontaneous abortion.

Initiation timing and dosage use of LDA

Although we did not find any difference in the occurrence of APOs based on LDA usage, the beneficial role of LDA in reducing the risk of preeclampsia is well established among high-risk pregnancies, not specifically but including all SLE pregnancies (20, 21). Therefore, we further analyzed the APOs within the LDA-prescribed group to determine if the initiation timing or the dosage of LDA was associated with the occurrence of APOs.

TABLE 2 Pregnancy outcomes among all patients with SLE and those without APS nor criteria aPL-positive patients.

All participants, including APS/criteria aPL positive patients					
		All (n = 75)	No LDA (n = 44)	LDA (N = 31)	P-value
pontaneous abortion prior to 10 weeks, n (%)		4 (5.3%)	2 (4.5%)	2 (6.4%)	0.99
Live birth, n (%)		68 (90.6%)	40 (90.9%)	28 (90.3%)	0.99
Birth weight (g)		2,635 (2,257–2,937)	2,640 (2,392–3,007)	2,580 (2,217–2,912)	0.41
APO	Intrauterine fetal death >12 weeks, n (%)	3 (4.0%)	2 (4.5%)	1 (3.2%)	0.99
	Preterm delivery, n (%)	13 (17.3%)	6 (13.6%)	7 (22.5%)	0.36
	Preeclampsia, n (%) (early onset: late onset)	16 (21.3%) (5:11)	10 (22.7%) (2:8)	6 (19.3%) (3:3)	0.78 (0.64:0.50)
	Low birth weight, n (%)	25 (33.3%)	14 (31.8%)	11 (35.4%)	0.80
	Total APO, n (%)	32 (42.6%)	18 (40.9%)	14 (45.1%)	0.81
Flare during pregnancy to postpartum, n (%)		8 (10.6%)	4 (9.0%)	4 (12.9%)	0.99
Excluding APS/criteria aPL-positive patients					
		All (n = 60)	No LDA (n = 42)	LDA (n = 18)	P-value
Spontaneous abortion prior to 10 weeks, n (%)		4 (6.6%)	2 (4.7%)	2 (11.1%)	0.57
Live birth, n (%)		54 (90.0%)	38 (90.4%)	16 (88.8%)	0.99
Birth weight, (g)		2,637 (2,271–2,955)	2,773 (2,395–3,030)	2,523 (2,138–2,750)	0.16
APO	Intrauterine fetal death >12 weeks, n (%)	2 (3.3%)	2 (4.7%)	0 (0%)	0.99
	Preterm delivery, n (%)	10 (16.6%)	5 (11.9%)	5 (27.7%)	0.14
	Preeclampsia, n (%) (early onset: late onset)	11 (18.3%) (8:3)	9 (21.4%) (7:2)	2 (11.1%) (1:1)	0.48 (0.41:0.99)
	Low Birth weight, n (%)	20 (33.3%)	13 (30.9%)	7 (38.8%)	0.55
	Total APO, n (%)	25 (41.6%)	17 (40.4%)	8 (44.4%)	0.77
Flare during pregnancy to postpartum, n (%)		7 (11.6%)	5 (11.9%)	2 (11.1%)	0.99

P-values for the comparison between LDA-prescribed pregnancies and non-prescribed pregnancies are shown. Fisher's exact test was used for categorical variables, and Mann-Whitney U-test was used for continuous variables. APO, adverse pregnancy outcomes.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

****$P < 0.0001$.

First, we analyzed the initiation timing of LDA and its relationship to APOs by dividing the patients into 2 groups: those who initiated LDA within 6 weeks of gestation, approximately when pregnancy is recognized or prior to conception, and those who started after 6 weeks (Table 3). We observed a significantly higher birth weight in the group that started LDA before 6 weeks compared to those who started after 6 weeks (2,643 g vs. 2,215 g, $p = 0.01$). Additionally, while the overall incidence of preeclampsia did not differ significantly between the 2 groups, early onset preeclampsia was significantly lower in the group that initiated LDA before 6 weeks compared to those who started after 6 weeks (0/19, 0% vs. 3/12, 25%, $p = 0.04$). Other outcomes, including the frequency of live birth, preterm delivery, low birth weight, and total APOs, did not differ significantly between the 2 groups.

Next, we examined the relationship between LDA dosage and APOs. We observed that in the group prescribed 100 mg of LDA, birth weight was significantly higher compared to the 81 mg group (2,285 g vs. 2,937 g, $p = 0.002$). Consistent with this finding, the incidence of low birth weight was significantly lower in the 100 mg LDA group compared to the 81 mg group (8/14, 57.1% vs. 3/17, 17.6%, $p = 0.03$). There were no significant differences in the occurrence of preeclampsia, including subtypes of preeclampsia, or intrauterine fetal death between the 2 dosage groups. However, the overall frequency of APOs was significantly lower in the 100 mg group compared to the 81 mg group (10/14, 71.4% vs. 4/17, 23.5%, $p = 0.01$) driven by a non-significant but consistently lower frequency of each individual APO analyzed. When comparing the initiation of LDA before 6 weeks of gestation with a 100 mg dosage to other usages, we observed significantly better birth weight (2,930 g vs. 2,315 g, $p = 0.001$), with less low birth weight (1/11, 9% vs. 10/20, 50%, $p = 0.04$), and less preterm delivery (0, 0% vs. 7, 35%, $p = 0.03$) (Supplementary Table S4).

In conclusion, our findings suggest that for pregnancies in women with lupus who are prescribed LDA, initiating this prophylactic treatment before 6 weeks of gestation may be more beneficial than the later initiation. Furthermore, a dosage of 100 mg appears to offer advantages over 81 mg in improving pregnancy outcomes.

Discussion

In this study, our primary aim was to elucidate the beneficial effect of LDA in pregnancies among patients with lupus, the majority of whom conceived without active organ involvement. Additionally, we aimed to investigate the optimal initiation timing and dosage of LDA. Our findings indicated no significant difference in the frequency of APOs among lupus pregnancies, regardless of APS diagnosis or the criteria aPL positivity. However, among lupus pregnancies prescribed LDA, earlier initiation and a dosage exceeding 81 mg appeared to be beneficial in mitigating the risk of APOs.

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TABLE 3 Comparison of the initiation timing and dosage of LDA on pregnancy outcomes.

Initiation timing of LDA				
		LDA before 6 weeks (n = 19)	LDA after 6 weeks (n = 12)	P-value
Spontaneous abortion prior to 10 weeks		2 (10.5%)	0 (0%)	0.50
Live birth		17 (89.4%)	11 (91.6%)	0.99
Birth weight		2,643 (2,515–2,945)	2,215 (1,720–2,682)	0.01*
APO	Intrauterine fetal death >12 weeks	0 (0%)	1 (8.3%)	0.38
	Preterm delivery	1 (5.2%)	6 (50%)	0.07*
	Preeclampsia (early onset: late onset)	3 (15.7%) (0:3)	3 (25%) (3:0)	0.65 (0.04*:0.26)
	Low birth weight	4 (21.0%)	7 (58.3%)	0.05
	Total APO	6 (31.5%)	8 (66.6%)	0.07
Flare during pregnancy to postpartum		3 (15.7%)	1 (8.3%)	0.99
Optimal dosage of LDA				
		LDA 81 mg (n = 14)	LDA 100 mg (n = 17)	P-value
Spontaneous abortion prior to 10 weeks		2 (14.2%)	0 (0%)	0.19
Live birth		11 (78.5%)	17 (100%)	0.09
Birth weight		2,285 (2,056–2,442)	2,937 (2,706–3,046)	0.002**
APO	Intrauterine fetal death >12 weeks	1 (7.1%)	0 (0%)	0.45
	Preterm delivery	5 (35.7%)	2 (11.7%)	0.19
	Preeclampsia (early onset: late onset)	4 (28.5%) (3:1)	2 (11.7%) (0:2)	0.36 (0.08:0.99)
	Low birth weight	8 (57.1%)	3 (17.6%)	0.03*
	Total APO	10 (71.4%)	4 (23.5%)	0.01*
Flare during pregnancy to postpartum		2 (14.2%)	2 (11.7%)	0.99

P-values for the comparison between different initiation timings (above), and different dosage (below) are shown. Fisher's exact test was used for categorical variables, and Mann-Whitney U-test was used for continuous variables. APO, adverse pregnancy outcomes.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

****$P < 0.0001$.

Behind our aim lies an ongoing discussion on whether all lupus pregnancies should receive prophylactic LDA therapy, irrespective of individual risk factors such as disease activity, lupus nephritis involvement, aPL profile, and other concomitant risk factors (4, 11). Due to our small sample size, our results did not provide clear evidence of LDA benefits or identify specific risk factors associated with LDA efficacy. Consistent with our findings, previous multicenter prospective cohort data (4), which evaluated APO risks in patients with stable lupus, found no difference in APOs irrespective of LDASA use, consistent with our findings. Similarly, another multicenter retrospective study reported comparable results among patients with SLE without high-risk factors such as lupus nephritis and aPL positivity (11). Our findings align with these studies, highlighting the heterogeneity among lupus pregnancies and the need for risk stratification to determine the necessity of LDA. This underscores the importance of disease control at conception and the necessity for risk stratification when planning pregnancies in patients with SLE, in addition to the use of LDA (8, 12).

Another important point regarding LDA requirements is the substantial disparity between LDA prescription rates and guideline recommendations (8, 12). In our study, the prescription rate was 39.6%, which is below half of the recommended level. Similarly, an international cohort study reported LDA usage at 25%, regardless of aPL status (22). While we did not conclusively demonstrate the benefits of LDA prescription among SLE pregnancies with stable disease activity, the incidence of APOs, notably preeclampsia (21.3% overall; 18.3% without APS/aPL positivity), exceeded the prevalence reported in the general population (1%–5.6%) (5, 23). This highlights the necessity for LDA administration in specific patients with SLE during pregnancy. In addition to the gap between recommendations and actual LDA prescription rates, the use of hydroxychloroquine, also recommended for management pregnancies in lupus (8), was notably low in our study (17.3%). Similar to this percentage, previous multicenter cohort data of SLE patients from Japan reported a low hydroxychloroquine prescription rate of 18.3% (24). A study investigating the reasons for this low prescription rate in Japan, compared to other countries, pointed to the influence of the 1974 withdrawal of chloroquine from the Japanese market due to cases of retinopathy (25). Given the accumulating evidence of the safety and efficacy of hydroxychloroquine in lupus pregnancies (26) both physicians and patients need to be better informed to facilitate its use among women of childbearing age.

Additionally, in our data, APS diagnosis and aPL positivity were the primary reasons for prescribing LDA in lupus patients, while non-criteria aPL positivity played a lesser role in decisions regarding LDA use in pregnancies without lupus nephritis. Given the established inclusion of LDA in standard APS management during pregnancy (8, 12), these findings are unsurprising. However, in non-criteria aPL positive patients, our results suggest that, besides aPL positivity, multiple risk factors, particularly concomitant lupus nephritis, may

influence physician's decision to prescribe LDA in lupus pregnancies. Until we can accurately stratify which subset of pregnant patients with lupus truly require LDA, we believe there are significant benefits of LDA use during pregnancy based on risk-benefit consideration and cost-effectiveness (8), which warrant further investigation.

The second point highlighted by our data is the discussion regarding the optimal timing for initiating LDA and determining its dosage. Despite LDA being recommended for all SLE pregnancies by clinical guidelines such as those from The American College of Obstetricians and Gynecologists (ACOG) (27), National Institute for Health and Care Excellence (NICE) (28), International Society for the Study of Hypertension in Pregnancy (ISSHP) (29), and ACR (8), guidance on dosage and initiation timing vary slightly among guidelines. The ACOG suggests LDA 81 or 100 mg before the first trimester (27), a dosage the same as ACR, which recommends LDASA 81 or 100 mg starting from 12 to 16 weeks of gestation (8). On the other hand, NICE recommends 75 mg–150 mg from 12 weeks (28), and ISSHP advises 75–162 mg before 16 weeks (29) (Supplementary Table S5). Due to uncertainties regarding the optimal dosage of LDA, a meta-analysis comparing aspirin doses of 75–81 mg vs. 150–162 mg has been conducted, indicating that higher doses are significantly associated with a reduction in preeclampsia risk compared to lower doses (30). However, the scarcity of high-quality evidence highlights the challenges faced in conducting cohort studies and clinical trials among pregnant patients with rheumatic diseases (31). Therefore, we advocate for further research that includes diverse racial and ethnic populations to elucidate the optimal LDA dosage and its appropriate application in SLE pregnancies.

Not only the dosage of LDA but also the timing of its initiation remains a question. Clinical guidelines generally recommend initiating LDA between 12 and 16 weeks of gestation (8, 12, 27–29). However, our data indicated significant improvements in birth weight and a reduction in the frequency of early-onset preeclampsia among pregnancies that began LDA before 6 weeks of gestation compared to those with later initiation. Considering the distinct pathophysiology of early-onset preeclampsia in contrast to late-onset preeclampsia, where early-onset preeclampsia is primarily due to defective placentation, and placental development begins as early as the end of third week post-fertilization (23, 32), it may be reasonable to initiate preventative therapy early in high-risk pregnancies related to placentation issues. This, however, requires further investigation. Furthermore, the importance of preconception care among lupus pregnancies, as well as planned pregnancies (8, 12), potentially facilitates early LDA initiation and improves compliance.

This study has several limitations. First, the data only includes Japanese patients. Racial disparities are one of the important factors that influence disease activity among patients with lupus and pregnancy outcomes (1, 27). Although we highlighted several important points, further studies employing more diverse populations are necessary. Second, the study's small sample size and its single-center, retrospective design limits its generalizability. The small sample size made it challenging to accurately adjust for individual risk factors across multiple pregnancies included in the study. For instance, multiple occurrences of preeclampsia in the same patient may have contributed to the high rate of preeclampsia observed in our data. Additionally, although numerous known risk factors are associated with APOs in lupus pregnancies, we were unable to account for them through multivariable analysis due to the limited sample size. Instead, we performed analyses excluding the most significant factors, such as lupus nephritis, APS, and criteria aPL positivity. Consequently, the results should be interpreted with caution due to the small sample size available for comparison. Furthermore, our study lacked specific criteria for physician's decisions regarding LDA prescription and dosage. Beyond APS and criteria aPL positivity, the reasons for LDA prescription were unclear, along with the low prescription rates. These real-world practice conditions, including low hydroxychloroquine prescription rates, and insufficient steroid tapering, may have also biased the results.

Despite these substantial limitations, which challenge the generalizability of our findings, we believe our study addresses a critical and realistic issue in lupus pregnancy management. To the best of our knowledge, this is the first report assessing the optimal dose and initiation timing for managing lupus pregnancies. Larger studies are needed to validate these findings, which we believe will be meaningful in optimizing care and enhancing outcomes for lupus pregnancy.

In summary, our findings highlight 2 key points. First, the beneficial effects of LDA on all pregnancies among patients with lupus were not conclusively identified, suggesting the critical need for individualized risk stratification. Second, while further investigation is warranted, our data suggest that exploring the optimal dosage and timing of LDA administration may enhance pregnancy outcomes in patients with SLE. Future research should therefore focus on refining these variables to inform more personalized treatment strategies and improve management approaches for pregnancies in patients with SLE.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Clinical Research Ethics Review Committee, University of Tsukuba Hospital, (approval number: H29-154). The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because because of the retrospective and observational design that used only clinical data obtained through daily clinical practice.

Author contributions

SA: Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal Analysis, Data curation, Conceptualization. HT: Writing – review & editing, Supervision, Funding acquisition. MY: Writing – review & editing, Data curation. AO: Writing – review & editing, Data curation. AK: Writing – review & editing, Data curation. HM: Writing – review & editing, Data curation. HA: Writing – review & editing, Data curation. YK: Writing – review & editing, Data curation. IM: Writing – review & editing, Supervision, Funding acquisition, Data curation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/flupu.2024.1470870/full#supplementary-material

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Development of a risk prediction model for the first occurrence of thrombosis in patients with OAPS

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Objectives: The aim of this study is to assess the risk factors associated with thrombotic events in obstetric antiphospholipid syndrome (OAPS) patients and to develop a predictive model specifically tailored to predict the risk of postpartum thrombosis in OAPS patients without prior thrombotic events. This research seeks to enhance clinician's awareness regarding the postpartum care and monitoring of OAPS patients.

Methods: A retrospective study was conducted at the First Affiliated Hospital of the Fourth Military Medical University including 269 consecutive inpatients diagnosed with antiphospholipid syndrome (APS) from July 1, 2008 to July 31, 2022. All participants met the 2006 Sydney APS classification criteria or the "non-criteria OAPS classification". Out of 98 candidate clinical and laboratory parameters considered, 40 potential variables were selected for analysis based on expert opinion. The logistic regression mode with the Least Absolute Shrinkage and Selection Operator (LASSO) were used to identify optimal predictive characteristics. All samples were included in the model building and a nomogram was generated based on these characteristics. The differentiation, calibration, and clinical utility of the predictive model were evaluated using the area under the curve (AUC), calibration curve, and decision curve analysis. The model was also validated by a 1000 bootstrap tests.

Results: 126 patients with OAPS were enrolled, and a total of 89 OAPS patients who had never experienced thrombosis were retrospectively analyzed. After 3 years follow-up, 32.58% of the patients (29/89) developed thrombosis. In order to create, LASSO logistic regression identified three optimal variables: the platelet count less than 125×109/L, more than one positive aPLs (antiphospholipid antibody), and the use of low molecular weight heparin (LMWH) or low dose aspirin (LDA) after delivery. A predictive model was conducted using these three predictive indicators for patients with OAPS who experience thrombosis for the first-time. This prediction model has good distinction, good calibration, and fair clinical practicality.

Conclusion: Our model has good predictive ability in assessing the risk of thrombosis in patients with OAPS without prior thrombotic events. This model is easy to predict, has good discriminability and calibration, and can be utilized as a routine tool for thrombus screening in OAPS patients.

KEYWORDS

antiphospholipid syndrome, thrombosis, obstetric antiphospholipid syndrome, antiphospholipid antibodies, nomogram

1 Introduction

Antiphospholipid syndrome (APS), including thrombotic antiphospholipid syndrome (TAPS) and obstetric antiphospholipid syndrome (OAPS), is an autoimmune disease associated with recurrent thrombosis and morbid pregnancy. It is characterized by concomitant persistence of antiphospholipid antibodies at serum levels of moderate to high titer (1). In severe circumstances, thrombosis can lead to disability or even death for a patient, severely impairing their quality of life. Some patients with obstetric antiphospholipid syndrome may develop thrombosis sometime after delivery. However, there is currently no reliable method to identify these high-risk populations.

Currently, the GAPSS (Global Antiphospholipid Syndrome Score) and aGAPSS (adjusted Global Antiphospholipid Syndrome Score) are mainly used for prediction of thrombosis risk in patients with antiphospholipid syndrome (2). Because the GAPSS score includes an antibody to PS/PT (phosphatidylserine/prothrombin), which is infrequently used in laboratory testing, the aGAPSS score is more commonly used clinically. On the other hand, little is known about how well aGAPSS predicts thrombosis in patients with OAPS (no history of thrombotic events). Several studies have investigated predictors of APS prognosis, but risk factors vary greatly in study designs, patient selection criteria and aPLs profiles (3). Platelets play an important role in the pathogenesis of antiphospholipid syndrome, interacting with the components of the coagulation system and the immune system, such as neutrophils and lymphocytes. The 2023 ACR/EULAR Antiphospholipid Syndrome Guideline has already included clinical manifestations such as thrombocytopenia as one of the inclusion criteria in the APS classification (4).

Our study evaluated the risk factors for thrombosis in OAPS patients with a history of obstetric events only (no previous thrombotic events). We aimed to develop a prediction model to predict the risk of thrombosis in these patients. The goal is to emphasize the importance of postpartum follow-up in OAPS patients for clinicians. At the same time, this model was compared with the aGAPSS score, and its predictive value for thrombosis was assessed.

2 Method

2.1 Patient assessment and data collection

This study retrospectively included 269 consecutive APS patients admitted to the First Affiliated Hospital of the Fourth Military Medical University (Xijing Hospital) from July 2008 to July 2022. Among them, 115 were OAPS patients with a history of obstetric events only (no previous thrombotic events). All participants met the 2006 Sydney APS classification criteria or the non-criteria OAPS classification (1, 5). Exclusion criteria:1) thrombotic events prior to the onset of OAPS; 2) presence of other coagulation disorders, such as severe liver disease and malignancy; 3) patients with follow-up <1 year; 4) incomplete medical records. Follow-up time to the endpoint was calculated from the baseline to the date of diagnosis of thrombosis or to the last follow-up visit before the end of the study period (31 July 2023) for patients who did not develop thrombosis. Follow-up was censored at the time of the patient's last visit if the patient died of other causes or was lost to follow-up. The final population eligible for thrombosis risk analysis included 89 patients (Figure 1). The study was conducted in accordance with the Declaration of Helsinki and good clinical practice.

Before developing the predictive model, we analyzed previous research and clinical data to identify potential factors influencing the outcome. We also incorporated our insights to identify unstudied factors. The variables include: 1) demographic characteristics such as age, gender, ethnicity, and education level; 2) past medical history, including autoimmune diseases (e.g., systemic lupus erythematosus, Sjögren's syndrome), hypertension, diabetes, hyperlipidemia, and risk factors like smoking and alcohol consumption; 3) hospital laboratory indicators, such as blood tests, biochemical tests, coagulation function, and autoantibody series; 4) imaging indicators, including CT, MRI, and ultrasound; 5) clinical manifestations, including specific circumstances related to thrombosis and adverse pregnancy during disease onset; and 6) medication usage, such as long-term low-dose aspirin, low-molecular-weight heparin, and hydroxychloroquine sulfate. Demographic and clinical information at baseline were collected

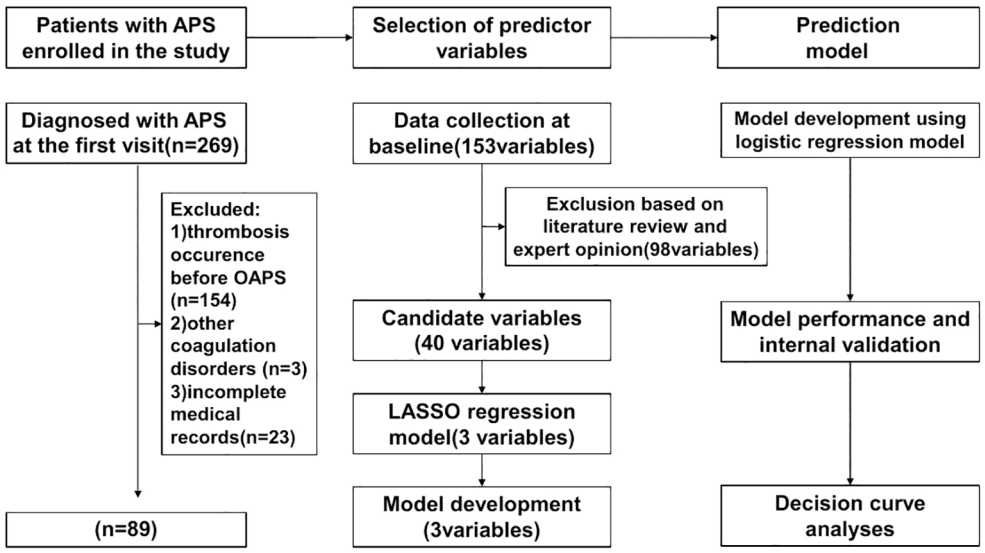

FIGURE 1
Flowchart for constructing the first occurrence of thrombosis in the OAPS prediction tool.

by trained researchers from electronic medical records. Patients were followed up through telephone interviews or outpatient visits to monitor their actual medication use and vascular thrombotic events. They were required to be followed up for at least one year. Patients were fully evaluated and documented every 3 to 12 months.

Hypertension was defined as having high blood pressure or using antihypertensive medication at two or more random time points. Diabetes mellitus was defined as having two or more fasting blood glucose levels > 7.0 mmol/L or using insulin or oral hypoglycemic agents. Smoking status was determined by self-reporting of tobacco consumption. Serum total cholesterol and HDL cholesterol levels were determined using standardized enzymatic methods and interpreted based on current threshold values.

2.2 Detection of aPLs

Plasma and serum samples were collected from patients and all aPLs tests were performed in our laboratory. The aPLs profile includes lupus anticoagulant (LA), anti-β2 glycoprotein I antibody (anti-β2GP1), and anticardiolipin antibody (aCL). Autoantibodies aCL and anti-β2GP1 were detected by ELISA. In our study, we did not conduct separate tests for the IgM and IgG subclasses of aCL and anti-β2GPI antibodies due to limitations in the hospital's testing methods. Therefore, according to our laboratory's reference interval, a positive result is defined as: aCL > 40 IU/mL and aβ2GPI > 40 RU/mL. Plasma samples were tested for the presence of LA according to the criteria recommended by the ISTH Lupus Anticoagulant/Antiphospholipid Dependent Antibody Subcommittee. Plasma sample was considered positive for LA if the Dilute Russell's Viper Venom Test (dRVVT) ratio was > 1.2 (6). Only tests for aPLs diagnosed at least 12 weeks apart were considered positive.

2.3 Assessment of thrombosis

Thrombosis was diagnosed by two experienced immunologists based on clinical presentation and imaging findings (magnetic resonance imaging or computed tomography angiography or vascular ultrasound). Arterial thrombotic events included stroke, myocardial infarction, and arterial occlusion, were confirmed by computed tomography (CT), magnetic resonance imaging, conventional angiography, or vascular ultrasound. Venous thrombosis was defined as deep vein thrombosis and pulmonary thrombosis, and confirmed through CT scan, angiography or vascular ultrasound.

2.4 aGAPSS score

The aGAPSS was calculated by summarizing the corresponding risk factors: score 1 for arterial hypertension, score 3 for hyperlipidemia, score 4 for ab2GPI, score 4 for LAC, and score 5 for aCL.

2.5 Statistical method

The methods in this study were followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement. Continuous variables are reported as medians (interquartile range [IQR]) and categorical variables as frequencies. Statistical analyses were performed using the Mann-Whitney U test, Fisher exact test or chi-squared test, as appropriate. P values less than 0.05 were considered significant. Least absolute shrinkage and selection operators (LASSO) were used to select the most predictive among the candidate variables. Based on these independent predictors, a nomogram was constructed and the area

under the receiver operating characteristic (AUROC) curve was plotted to evaluate and compare the discriminative power of the nomogram with that of the aGAPSS. The AUC was calculated to compare the accuracy of the model parameters between different cut-off values.

Internal cross-validation of the predictive model was performed using the bootstrap method. The predictive performance of the model was assessed using Harrell's consistency index (C-index) and calibration curves to validate model discrimination and calibration. Decision curve analysis was then used to assess the clinical benefit of our model. The two-sided P values for all statistical tests were < 0.05 and the differences were statistically significant. All statistical analyses were performed using IBM SPSS Statistics (version 25.0) and R software (version 4.3.1).

The main steps on developing a clinical prediction model are illustrated in the flowchart (Figure 1): First, initial variables were determined by combining literature research and clinical experience. Then, the predictive factors were identified through LASSO regression. Using these predictive factors, we created the prediction model and visualized it with a nomogram. Subsequently, the model was validated for performance and compared with the efficacy of previous relevant models.

3 Result

3.1 Baseline characters of the population

During the study period, there were a total of 269 patients initially identified as APS. According to the exclusion criteria, 89 patients were ultimately retained for analysis, with 154 patients were excluded if they had only thrombosis or thrombosis prior to the onset of OAPS, 3 patients were excluded due to other coagulopathies (2 with malignancy and 1 with severe liver disease), and 23 patients were excluded due to incomplete medical records. The average onset age of 27.34 ± 3.62 years.

During a mean follow-up of 3 years, 29 cases (32.58%) of patients with OAPS developed a new thrombus. We compared the baseline demographics, clinical characteristics and laboratory tests between those thrombotic patients with non-thrombotic patients (Table 1).

TABLE 1 Demographic and clinical characteristics of OAPS patients in the thrombotic vs non-thrombotic group.

Variables	Total (n = 89)	thrombotic (n = 60)	Non- thrombotic (n = 29)	p
Onset age,years	27.34 ± 3.62	27.73 ± 3.49	26.52 ± 3.81	0.154
Follow-up duration, years	3 (1, 6)	3 (1.19, 4.25)	3 (1, 9)	0.578
SLE, n (%)	35 (39)	19 (32)	16 (55)	0.058
nonstandard, n (%)	38 (43)	20 (33)	18 (62)	0.019
HP, n (%)	19 (21)	9 (15)	10 (34)	0.068
HLP, n (%)	20 (22)	9 (15)	11 (38)	0.031
ab2GP1, n (%)	62 (70)	38 (63)	24 (83)	0.105
LAC, n (%)	32 (36)	18 (30)	14 (48)	0.148
aCL, n (%)	52 (58)	30 (50)	22 (76)	0.037
morbidfrequency, n (%)				0.572
1	22 (25)	16 (27)	6 (21)	
2	40 (45)	26 (43)	14 (48)	
3	14 (16)	11 (18)	3 (10)	
4	10 (11)	6 (10)	4 (14)	
5	2 (2)	1 (2)	1 (3)	
6	1 (1)	0 (0)	1 (3)	
heart, n (%)	27 (30)	14 (23)	13 (45)	0.069
plt, Median (Q1,Q3)	134 (84, 203)	159.5 (121.5, 222)	86 (61, 114)	< 0.001
PLT125, n (%)	42 (47)	16 (27)	26 (90)	< 0.001
IgG, n (%)	21 (24)	15 (25)	6 (21)	0.855
IgM, n (%)	6 (7)	4 (7)	2 (7)	1
IgA, n (%)	11 (12)	7 (12)	4 (14)	0.744

(Continued)

TABLE 1 Continued

Variables	Total (n = 89)	thrombotic (n = 60)	Non- thrombotic (n = 29)	p
C3, n (%)	45 (51)	26 (43)	19 (66)	0.083
C4, n (%)	44 (49)	24 (40)	20 (69)	0.02
aPLs2o3, n (%)	43 (48)	21 (35)	22 (76)	< 0.001
PLDAorLMWH, n (%)	70 (79)	52 (87)	18 (62)	0.017
DLDAorLMWH, n (%)	43 (48)	32 (58)	8 (28)	0.013
IVIG, n (%)	22 (25)	16 (27)	6 (21)	0.726
Phormonotherapy, n (%)	51 (57)	34 (57)	17 (59)	1
Pimmunosuppressor, n (%)	34 (38)	21 (35)	13 (45)	0.508
PHCQ, n (%)	59 (66)	41 (68)	18 (62)	0.729
mono1, n (%)	25 (28)	20 (33)	5 (17)	0.183
neutro1, n (%)	32 (36)	25 (42)	7 (24)	0.168
lym1, n (%)	33 (37)	16 (27)	17 (59)	0.007
mpv1, n (%)	29 (33)	17 (28)	12 (41)	0.322
pdw1, n (%)	44 (49)	30 (50)	14 (48)	1
pt1, n (%)	26 (29)	14 (23)	12 (41)	0.132
aptt1, n (%)	42 (47)	26 (43)	16 (55)	0.411
fib1, n (%)	49 (55)	37 (62)	12 (41)	0.115
pta1, n (%)	60 (67)	44 (73)	16 (55)	0.141
inr1, n (%)	39 (44)	30 (50)	9 (31)	0.144
ddi1, n (%)	53 (60)	38 (63)	15 (52)	0.415
fdp1, n (%)	14 (16)	8 (13)	6 (21)	0.371
aGAPSS, Median (Q1,Q3)	8 (4, 10)	5 (4, 9)	10 (8, 13)	< 0.001
aGAPSSover10, n (%)	28 (31)	13 (22)	15 (52)	0.009

3.2 Development of predictive models

3.2.1 Selection of predictor variables

After data collection, we found 98 potentially correlated variables. To enhance clinical practice, it is vital that the chosen parameters are readily accessible. Consequently, after discussions among the three corresponding authors, we eliminated variables like lymphocyte subsets and cytokines, focusing on 40 potential candidate variables (Figure 1). To avoid overfitting, we utilized the Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression to choose the most predictive variables from the 40 potential candidate variables preselected based on expert opinion (Figure 2). Before including them in the final model, the regression model was built by considering the number and appropriateness of the predictor variables selected. Based on the number of variables displayed by lambda.1se, the three predictor variables were selected to develop the model and estimate the coefficients associated with each significant predictor variable.

3.2.2 Construction of nomogram

Based on these independent predictors, we constructed a predictive nomogram for first-time thrombosis in OAPS using the rms package of the R software (Figure 3). A nomogram is a graphical tool used to visually represent a predictive model, illustrating the relationships between variables. It is derived from the results of multifactorial regression analysis. Each variable is plotted alongside its corresponding score on a unified scale. In clinical practice, doctors can use the nomogram by determining the values of the predictors for each patient and following these steps: First, assign scores to each predictor's value based on the nomogram's scale. Next, sum all the scores to obtain a total score. Finally, use this total score to find the corresponding risk prediction value on the nomogram. For each patient diagnosed with purely OAPS, we summed the scores from the three identified risk factors. The probability of the patient's risk of a thrombotic event was then determined based on the "total points" axis of the nomogram. We have provided an example of the clinical application of the nomogram in the Supplementary Material (Supplementary

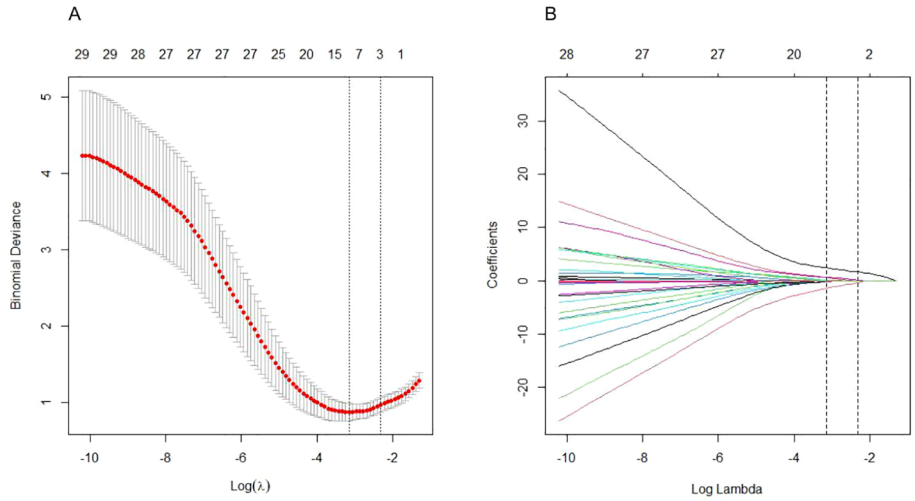

FIGURE 2
Clinical feature and laboratory parameter selection using the LASSO logistic regression model. **(A)** Optimal parameter (lambda) selection by LASSO used tenfold cross validation via minimum criteria. The average number of predicted variables is expressed as a number along the upper x-axis. The average deviation of each model is represented by a red dot, and the upper and lower limits of the deviation are represented by vertical lines passing through the red dot. The best value of lambda is defined by a vertical black line (λ=0.054). **(B)** LASSO coefficient profiles of the variables plotted against the log(lambda) sequence. Drawing vertical lines by optimum lambda values of three nonzero coefficients through tenfold cross-validation.

Figure S1), demonstrating how to conduct risk assessment based on the specific conditions of a patient.

3.2.3 Construction of risk scoring and network calculator

A risk score for the first thrombosis in patients with OAPS was derived from the coefficients of the logistic model. We calculated the probabilities and 95% confidence intervals of the logistic model using the following formula. The risk of the first thrombosis in an individual patient with OAPS can be calculated using the following formula: prognostic index = 3.3058×PLT125 + 2.0162×aPLs2o3 - 2.8393×DLDAorLMWH. All variables were coded as dichotomous. Where DLDAorLMWH was negatively correlated with thrombosis, the other two predictors were positively correlated.

3.3 Model performance evaluation and internal validation

To assess and contrast the identification of the new model with aGAPSS, the area under the receiver operating characteristic (AUROC) curve was plotted. The AUC of the new model was greater than that of aGAPSS [0.9181(95% CI, 0.8634-0.9728) vs. 0.7848 (95% CI, 0.6899-0.8796), P<0.001], indicating that the new model has better discriminatory power (Figure 4). To ensure accurate prediction of column-line plots, calibration curves were created by plotting the observed probabilities against the predicted probabilities of the Noetherian plots. The two-sided p-values for all statistical tests were less than 0.05 and the differences were statistically significant (Figure 5). The Brier score of the model was 0.107. The comparison between predicted risk and observed outcomes is shown in 200 Bootstrap of calibration plots. Hosmer-lemeshow test is 0.083.

3.4 Net benefit of predictive modelling

The potential net benefit at different probability thresholds was assessed and compared through decision curve analysis (DCA) using the rmda software package (Figure 6). To compared

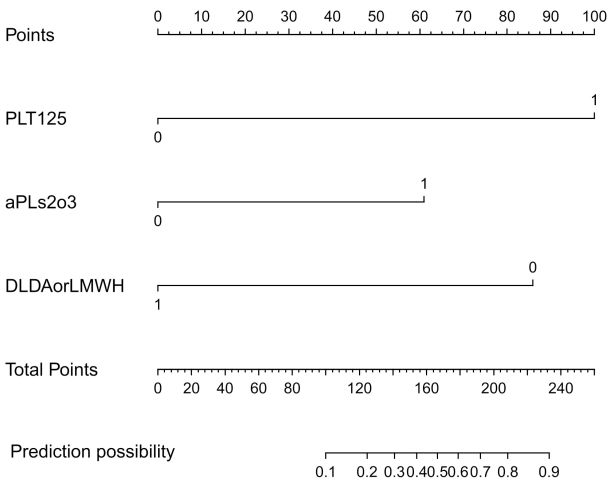

FIGURE 3
Plotting of nomogram according to predictors. This model was developed with PLT125, aPLs2o3, DLDAorLMWH. The scale of the line segment corresponding to each variable in the prediction model indicates the possible value range of the variable, and the length of the line segment indicates the influence of the factor on the outcome event. Point represents the individual score corresponding to each variable under different values, and the total score is obtained by adding the individual scores of all variables. Risk represents the risk of the first occurrence of thrombosis in patients with OAPS. PLT125: blood platelet less than 125×10^9/L; aPLs2o3: two or three aPLs are positive; DLDAorLMWH: patient receive LDA or LMWH after delivery.

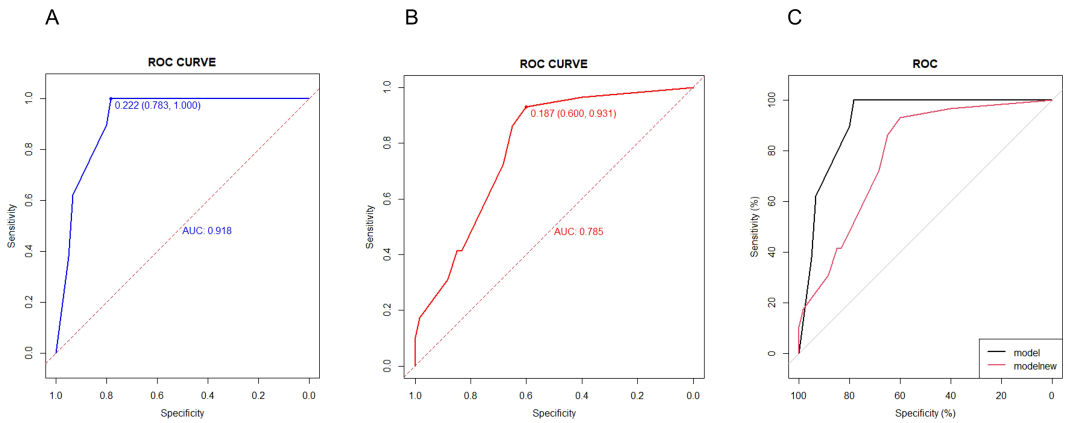

FIGURE 4
Efficiency and validation of the disease diagnosis model. **(A)** ROC of new model in OAPS patients (ROC of the first occurrence of thrombosis in patients with OAPS). **(B)** ROC of aGAPSS model in OAPS patients. **(C)** ROC of new model and aGAPSS model in OAPS patients.

screening based on whether all patients with OAPS would experience a thrombotic event or not, the DCA was performed. The curves from the predictive model showed positive net benefits for probability thresholds between 1% and 78%. This suggests that using the model to inform clinical decisions will lead to better outcomes for any decision in this range.

4 Discussion

The retrospective cohort study conducted at our center provides data to explore risk factors for the first-onset thrombosis in patients with OAPS, and to develop appropriate clinical prediction models. Our purpose is to develop a risk prediction model that is user-friendly for both clinicians and patients. In the internal validation of the study cohort, the model demonstrated satisfactory performance with an AUC-based accuracy of 0.9181. After appropriate calibration, the resulting nomogram was effective in predicting the risk of future thrombotic events in patients with OAPS alone. Decision curve analysis demonstrated that if the threshold probability of patients is between 1% to 78%, using this model to predict thrombosis events would provide more benefits compared to either the treat-all strategy or the treat-none strategy. The three variables required to calculate the risk of time to thrombosis in our prediction model are typically available at the time of the visit, and the user-friendly design of the network calculator facilitates its semless integration into routine practice. To our knowledge, this is the first clinical prediction model currently available for initial thrombotic events in APS patients with obstetric-only events. If a patient's estimated risk of a thrombotic event is low, clinicians may choose to follow up; however, if the risk is high, clinicians can be guided to screen for thrombosis in conjunction with the patient's clinical presentation.

Our study revealed that 32.58% (29/89) of patients with OAPS experienced thrombotic events during a median follow-up of 3 years. De Jesús, G. R. et al. conducted a multicenter retrospective study using the APS Clinical Trials and Consortium for International Networking (APS ACTION) clinical database and knowledge base. The study revealed that 63% (47/74) of women with OAPS experienced a thrombotic event after the initial obstetric onset, with an average time of 7.6 ± 8.2 years. A younger age at the diagnosis of OAPS, additional cardiovascular risk factors, superficial venous thrombosis, valvular heart disease, and multiple aPL positivity all increase the risk of a first thrombosis after pregnancy morbidity (7). The risk factors in this article did not include indicators such as complement, platelet, lymphocyte counts, and preconception pregnancy and perinatal medications, which recent studies have shown may be associated with the development of OAPS. In addition, the rate of thrombosis in this study was

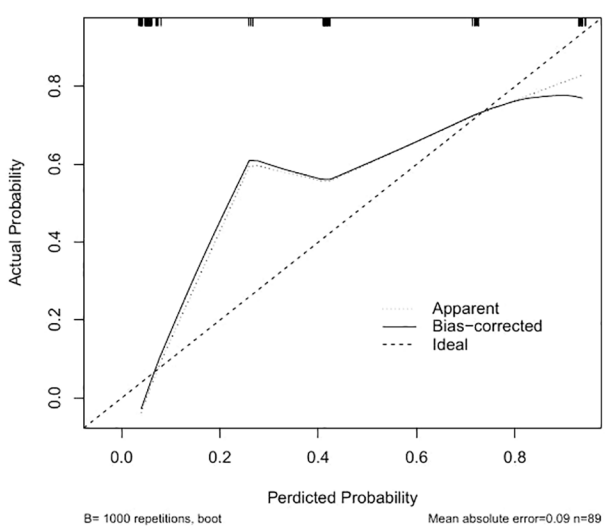

FIGURE 5
Creation of calibration plots of the new model. "Apparent" is the uncalibrated prediction curve, "Bias-correctrd" is the calibrated prediction curve, and "Ideal" is the standard curve, which represents the perfect prediction of the ideal model. The Y-axis represents the actual prevalence of the first occurrence of thrombosis in patients with OAPS. The X-axis represents the predicted risk of the first occurrence of thrombosis in patients with OAPS in the cohort.

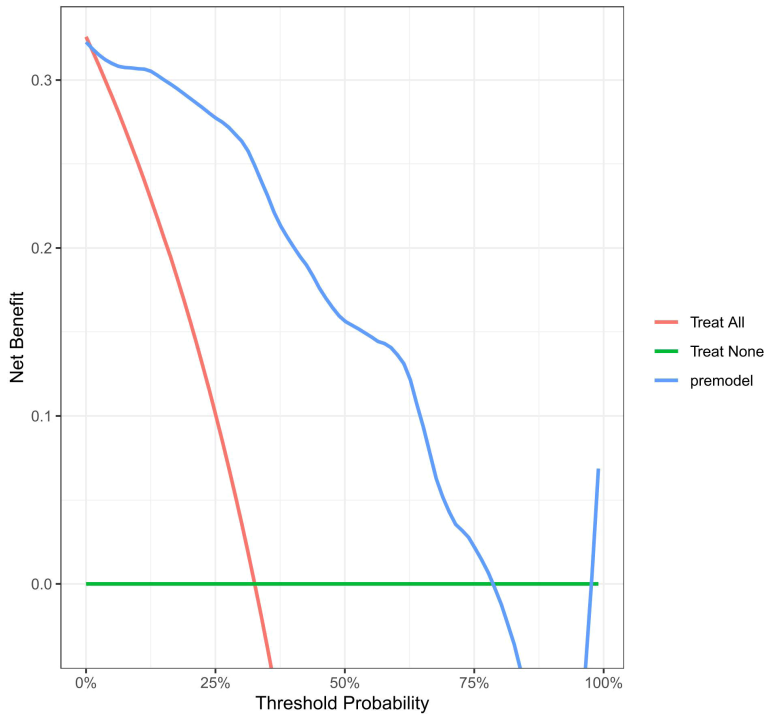

FIGURE 6
Decision curve for the model in predicting the first occurrence of thrombosis in patients with OAPS. Standard net benefit (y-axis) and risk threshold (x-axis) formed the coordinate system. The blue line represented our model, red line represented the assumption that all the people had occurred thrombosis after delivery, and green line represented the assumption that all the people hadn't occurred thrombosis after delivery.

higher than in our study, which may be related to the longer follow-up period. Silver et al. first reported that 15.7% of obstetric APS patients had thrombosis during a median follow-up of 3 years (8). The percentage was lower than in our study, possibly due to the inclusion of APS patients with pre-existing thrombosis before the study, and a higher percentage of prolonged anticoagulant use in the postpartum period compared to our study. A retrospective case-control study was conducted in 2005, 141 women with OAPS were matched with 141 women with idiopathic recurrent miscarriage. Most of the patients in the study reported that thrombosis occurred in the brain and were predominantly arterial (9). Our study also suggests that patients with OAPS have a higher risk of developing arterial thrombosis, particularly arterial cerebrovascular events. Therefore, it is recommended that patients be promptly evaluated for cerebrovascular events when they present with symptoms such as dizziness, headache, and numbness of the limbs.

The GAPSS is an internationally recognized thrombosis risk prediction score that comprises six items. The score was initially developed and validated in a group of patients with systemic lupus erythematosus and subsequently in patients with APS without SLE (2). In the aGAPSS, anti-APS/PT was removed to enhance clinical applicability. The clinical utility of the aGAPSS in assessing thrombosis risk in various clinical settings has been described and validated. Baseline characteristics of different patient groups explain the variations in aGAPSS thresholds. Although there is no precise cut-off value that distinguishes between low and high risk, aGAPSS may be a useful tool for assessing new thrombotic events in patients with APS and for guiding pharmacologic therapy in high-risk patients (3, 10–13). In our retrospective study, we found that patients with thrombosis had higher aGAPSS values compared to patients without thrombosis.

However, aGAPSS has limited ability to assess obstetric events (14), possibly because the pathogenesis of OAPS differs from the pathophysiological mechanisms of TAPS (15–17). Due to the specificity of OAPS, which involves obstetric pathophysiologic mechanisms in addition to the common risk factors for thrombosis, our study also included variables related to adverse pregnancies. In our study, the baseline variables included numerous risk factors that previous studies have suggested may be associated with thrombotic recurrence in patients with APS (18–21). By using LASSO regression, it was confirmed that thrombocytopenia, multiple aPLs, and the use of anticoagulants and antiplatelets after delivery was confirmed to be the strongest risk factors predicting thrombotic events in patients with OAPS. The final selection of predictors was confirmed by expert opinion in terms of clinical validity, feasibility, and applicability, and internally validated for stability. After comparison, the AUC of our new model predicting the occurrence of thrombosis in OAPS (0.918) was higher than the AUC of aGAPSS (0.785), and the difference was statistically significant.

In 2023, the ACR/EULAR published new classification criteria in the form of a scoring system that categorizes additional weighted criteria into six clinical and two laboratory domains (4). Several weighted criteria from the new 2023 version of the classification criteria were incorporated into the variables included in our study. Among the final predictors of thrombosis risk obtained from the

analysis of the study results, thrombocytopenia is also a new element that appears in the new classification criteria. Platelets are small, anuclear, multifunctional blood cells that play an important role in the pathogenesis of antiphospholipid syndrome (22, 23). Platelets play a crucial role in the development of APS by regulating coagulation, thrombosis, inflammation, and innate immunity. They also interact with components of the immune systems such as neutrophils and lymphocytes (24, 25). A study by X, Zeng et al. confirmed the correlation between PDW and thrombotic events in patients with APS, supporting the theory that platelet activation is an important mechanism of thrombosis in patients with APS (26). B, Artim-Esen's study showed that among aPLs-positive patients, those with a low platelet count were more likely to develop thrombosis (27).

This retrospective study focuses on patients diagnosed with OAPS from July 2008 to July 2022 in our hospital. At that time, the new classification criteria for APS had not yet been published, and the 2006 Sydney criteria were primarily used in clinical practice. We reviewed the new criteria and reassessed the patients in our study. Among the 89 patients previously diagnosed with purely OAPS, 61 patients (68.54%) met the new OAPS classification criteria. To assess compliance rates for the old and new classification criteria, we focused on adverse pregnancy events in patients who did not meet the new criteria. These events included: early fetal deaths from 10 weeks to 15 weeks and 6 days(2/89), as well as fetal deaths from 16 weeks to 33 weeks and 6 days without severe preeclampsia or placental insufficiency (5/89). According to the new criteria, each of these items is assigned a value of 1 point, while a minimum score of 3 points is required for the clinical domain. Based on our inclusion criteria, 21 patients with non-standard obstetric antiphospholipid syndrome were also analyzed (21/89). Hence, they do not comply. It is crucial to conduct further research to compare the performance of the old and new classification criteria in clinical settings and to validate their effectiveness across various populations.

Increasing evidence suggests that each aPL is associated with a high risk of thrombosis, and complete antiphospholipid antibody profiling may better identify patients at risk than a single test. Therefore, risk stratification based on the number of positive tests has been proposed (18, 20, 21), and our data support this approach. Pengo et al. analyzed data from 618 consecutive patients over 6 years and found that triple-positive patients had the highest risk of thrombosis. They were also associated with a high risk of pregnancy morbidity, which was not seen in single-positive aPL (28). A prospective cohort study in Finland showed that double- or triple-positive aPLs was a risk factor for future thrombotic events, especially in individuals with underlying autoimmune disease, while being single-positive did not appear to increase the risk of thrombosis (29). Therefore, the combined use of aPL testing should be considered when discussing the risk of thrombosis in patients with OAPS.

According to the guidelines, women who receive LDA and prophylactic doses of LMWA prenatally should be treated with low-molecular-weight heparin continuously for 6 weeks postpartum (30, 31). Combined antiplatelet and anticoagulant therapy reduces the rate and prolongs the time to thrombotic recurrence in patients with APS associated with arterial thrombosis compared with monotherapy (30–34). The puerperal period carries an increased risk of thrombosis. Our research recorded thrombotic events in four patients during the puerperium, including two cases of cerebral infarction and two cases of deep vein thrombosis in the lower limbs. Our data indicate that patients with Obstetric Antiphospholipid Syndrome (OAPS) are at a higher risk of thrombosis during the puerperal period compared to the general population (35, 36). In our study, only 48% of patients were treated with LDA and/or LMWA in the postoperative period, which may be one of the reasons for the higher rate of thrombosis than in other studies (37). This further emphasizes the importance of thrombosis prevention in OAPS patients during the puerperium. We believe that these data analyses can provide valuable reference for clinical practice. It also suggests that rheumatologists need to communicate more with obstetricians and gynecologists about the latest academic advances in postpartum treatment and follow-up of OAPS (38).

The predictive model we developed in this study has some limitations: 1) this is a single-center, retrospective study with a small sample size, which may limit the generalizability of the prediction model to other regions. Therefore, further large sample studies are needed to confirm our model and measure its performance, especially its applicability to other regions and ethnicities; 2) the results of this study were evaluated through internal validation of the model and not have not been validated by external data sets. Multicenter external validation in other regions should be completed at a later date to further assess the performance of the model; 3) Other predictors, such as cytokine levels and lymphocyte subpopulation counts, were not included in the current study due to the high level of missing data. These variables should be investigated by including them in future prospective studies; 4) The 2023 ACR/EULAR APS classification criteria emphasize the importance of distinguishing between the IgG and IgM isotypes of aCL and anti-β2GPI antibodies (4). Our study could not perform separate tests for the IgM and IgG isotypes of aCL and anti-β2GPI antibodies because of hospital testing limitations. This limitation may affect our sensitivity in predicting thrombotic events and decrease the positive predictive value. We will implement modified testing methods to differentiate antibody isotypes in the future. We will establish medium and high titer thresholds for aCL and anti-β2GPI antibodies in the local population. These thresholds will be incorporated into our upcoming observational clinical studies. Additionally, we will conduct additional analyses to evaluate how antibody isotypes and the number of positive results influence the risk of thrombosis and pregnancy complications in APS patients.

Our study also has several advantages. Firstly, it was more targeted than previous studies, focusing solely on a subset of OAPS patients with only obstetric events. Secondly, we aimed to create a screening tool for clinical use. This predictive model mainly incorporates available clinical information and routine laboratory test results as variables. Thirdly, we excluded variables such as erythrocyte sedimentation rate or C-reactive protein level, which may change within a short period of time. We also converted most of the numerical variables to dichotomous variables, thereby reducing inconsistent observations of numerical fluctuations during the follow-up period.

In conclusion, we developed a risk prediction model using routine clinical assessments. Three risk variables included

PLT125, aPLs2o3 and DLDAorLMWH constructed a prognostic scoring index, and this new tool may effectively predict the future risk of thrombotic events in OAPS patients with a history of obstetric events only (without prior thrombotic events). Based on the net benefit and predictive probability thresholds, we recommend annual screening for high-risk patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Xijing Hospital of Fourth Military Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JG: Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing. YZ: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. ZW: Data curation, Investigation, Writing – original draft, Writing – review & editing. JJ: Investigation, Software, Validation, Writing – review & editing. JW: Validation, Writing – original draft. QH: Investigation, Writing – review & editing. XZ: Investigation, Writing – original draft. RL: Investigation, Writing – original draft. ZZ: Supervision, Writing – review & editing. KW: Supervision, Writing – review & editing. PZ: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

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Supplementary material

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Pregnancy planning in lupus and APS patients

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Systemic Lupus Erythematosus (SLE) and Antiphospholipid Syndrome (APS) have a substantial impact on pregnancy outcomes and require meticulous planning and management. This article explores the complex interrelationships between SLE, APS, and pregnancy and provides an overview of the associated risks and predictors. The crucial role of pre-conception counselling, risk stratification and tailored treatment plans is highlighted, accompanied by a suggested practical approach. Recent advancements in therapeutic approaches and emerging research on promising targeted interventions indicate the potential for enhanced maternal and fetal outcomes.

KEYWORDS

Systemic Lupus Erythematosus, Antiphospholipid Syndrome, pregnancy, pregnancy counselling, obstetric outcomes

1 Introduction

Systemic Lupus Erythematosus (SLE) primarily affects women of childbearing age. With ongoing advancements in treatment, patients may anticipate attaining a near-normal quality of life, wherein family planning may assume a pivotal role. Among rheumatic diseases, SLE has a distinctive interaction with pregnancy, as both can exert a detrimental influence on one another. This is particularly relevant for the approximately 40% of SLE patients who present with antiphospholipid antibodies (aPL) or secondary Antiphospholipid Syndrome (APS) (1). APS is characterized by the occurrence of thrombosis and/or obstetric complications in the presence of aPL, including anticardiolipin antibodies (aCL), anti-b2 glycoprotein-I antibodies (ab2GPI), and lupus anticoagulant (LA) (2, 3).

For women with SLE and APS who wish to conceive, pregnancy counselling is of fundamental importance. It includes stratification and adjustment of risk factors, optimization of medication and individualized planning of antenatal care. This article outlines pregnancy planning considerations for patients with SLE and APS, drawing on current research and clinical guidelines.

2 Pregnancy outcomes in SLE and APS

The prognosis for women with SLE who wish to become pregnant has improved markedly in recent decades, with notable declines in both maternal and fetal mortality. However, the incidence of maternal and fetal morbidity rates remains higher than in the general population, carrying an increased risk of pre-eclampsia, miscarriage, fetal loss, stillbirth, preterm birth, intrauterine growth restriction (IUGR), and small for gestational age (SGA) infants (4, 5). Furthermore, there is a considerable risk of SLE

flares during pregnancy and, to a lesser extent, postpartum (6). Consequently, all pregnancies in SLE are considered high-risk pregnancies, though the level of risk can vary depending on disease severity, current activity and additional risk factors, both related to and independent of SLE (7). A detailed discussion of this topic will be presented subsequently.

One of the most important additional risk factors is the presence of aPL. These antibodies are associated with an elevated risk of adverse pregnancy outcomes (APOs), including pre-eclampsia, thromboembolism, early and late pregnancy loss, placental insufficiency, IUGR, preterm delivery, and perinatal mortality (8). Depending on the data source and the population included, the live birth rate in women with untreated APS is around 50%, while it can be increased as high as 75%–85% with appropriate treatment according to recent guidelines (9, 10).

3 Predicting and modifying pregnancy outcomes

Given the complex nature of SLE, considerable effort has been made to identify reliable risk factors for individuals at increased risk prior to or during the early stages of gestation. The PROMISSE study marked a significant advancement in this field of research. The study provided baseline predictors of APOs in the 1st trimester, including the presence of LA (OR = 8.32), antihypertensive use (OR = 7.05), high disease activity with a PGA >1 (OR = 4.02), while non-Hispanic white ethnicity was identified as a protective factor (OR = 0.45). Among women without baseline risk factors, the APO rate was 7.8%, compared to 58% in those who were LA positive or non-white/Hispanic and undergoing antihypertensive treatment, which led to a fetal/neonatal mortality rate of 22% due to complications of prematurity (11). Other studies have shown that existing or previous lupus nephritis is a significant risk factor for unfavorable maternal and fetal outcomes (12, 13).

The PROMISSE study, in conjunction with other research, has demonstrated a correlation between reduced complement levels in the pre-conception or early gestational period and an increased risk of disease flares, pre-eclampsia, preterm delivery, and IUGR (14). This warrants close monitoring of complement dynamics for early detection of disease flares (15).

Disease activity of SLE at the time of conception is the single most important predictor for maternal and fetal morbidity, and it is modifiable. It is well established that achieving a low disease activity state (LDAS) or remission is crucial when planning a pregnancy (7). Active disease within 6–12 months before conception is associated with a two-fold increased risk of flares and maternal and fetal complications (16, 17). In recent years, new definitions of and a particular focus on remission and LDAS in SLE have emerged, raising the question of whether these states affect the outcome of our patients differently (18). Two international studies concluded that remission (as defined by DORIS) at conception is a stronger protective factor against relapse and complications during pregnancy than LDAS, with fewer relapses occurring in the 2 years postpartum (19, 20).

Hydroxychloroquine (HCQ) is another well-supported protective factor, with extensive empirical evidence for its ability to reduce the likelihood of both disease flares and APOs. Emerging evidence indicates that HCQ may be effective in preventing pre-eclampsia (21–23). In addition, HCQ is being investigated for its likely beneficial effect in refractory APS, which will be addressed in a later section.

This growing body of evidence highlights the importance of prenatal planning and the pursuit of disease remission before and throughout pregnancy in patients with SLE. Increasingly precise predictors of individual patient trajectories at the outset of pregnancy planning enable targeted interventions and closer monitoring for those at higher risk. At the same time, this facilitates the efficient distribution of healthcare resources, avoiding superfluous and potentially tedious diagnostic procedures for patients at relatively lower risk.

4 Pregnancy planning in SLE and APS

It is of utmost importance to inquire about the patient's perceptions of family planning at the appropriate time and in a repetitive manner. This is a crucial step in addressing several pivotal issues along the patient`s journey, even before the actual planning of the pregnancy. Several important topics must be addressed:

1. Contraception: When pregnancy is either undesired or must be postponed due to active disease or the need for teratogenic medication, it is essential to evaluate the most reliable and suitable contraceptive methods. Changes in medication provide an excellent opportunity for contraceptive counselling, a need underscored by the continued underuse of effective contraception in SLE patients (24, 25).
2. Fertility: Advances in SLE management, such as the use of gonadotropin-releasing hormone analogues (GnRHa), the Euro-Lupus regimen, and new therapeutic options, have mitigated infertility risks due to the gonadotoxic effects of cyclophosphamide (26). However, treatment can still indirectly impact fertility by delaying pregnancy to a time when ovarian reserve is declining. In both scenarios, fertility preservation options should be discussed, and referral to a gynecologist may be necessary.
3. Pregnancy: When pregnancy is desired, a comprehensive conception plan must be developed. From the patient's perspective, one of the primary objectives is to acquire knowledge on this special topic and to build their individual multidisciplinary network. Ideally, patients should be aware that pregnancy in these conditions will require foresight planning and in some cases a modification in medication or other measures, which may result in further postponement of their plans. This approach helps to avoid unplanned pregnancies and unfavorable maternal and fetal outcomes.

Effective pregnancy planning for women with SLE and APS necessitates consideration at multiple levels. An algorithmic approach, as illustrated in Figure 1 and outlined in the following section, can help to address these issues systematically and ensure thoroughness.

4.1 Step 1: evaluation of SLE disease activity

It is recommended that SLE should be in remission or at least in LDAS for 6 to 12 months prior to conception (7, 27). This range results from the varying severity of the disease. If the assessment reveals high disease activity, SLE must be treated following established guidelines and pregnancy must be postponed. In case of moderate disease activity, the objective of optimal disease control must take precedence over the possibility of conception. However, the rheumatologist can often use medication that is already compatible with pregnancy.

4.2 Step 2: medication management

All medication taken by the woman must be reviewed for safety during pregnancy. Compatible drugs should be continued throughout pregnancy with risks weighed against benefits for both mother and child.

Given its numerous beneficial effects on disease control and complications, it is recommended that HCQ may be continued (or started). Other disease-modifying anti-rheumatic drugs (DMARDs) with a favorable safety profile during pregnancy include azathioprine, cyclosporine and tacrolimus. While prednisolone is inactivated in the placenta and can be applied during pregnancy, prolonged use of doses above 7.5 mg/day has been associated with an increased risk of gestational diabetes, SGA babies, and a shorter gestational age (28).

There is growing evidence supporting the use of biologics such as belimumab and rituximab during pregnancy when clinically indicated. However, this is not yet sufficient to justify a general recommendation, and any decision to use these drugs during pregnancy must be made on a case-by-case basis. In approximately 500 pregnancies involving belimumab and approximately 300 pregnancies involving rituximab, respectively, no evidence of a teratogenic effect has been identified (29–32). A similar amount of data is available on ocrelizumab, a B-cell inhibitor that targets CD20 (32). The use of rituximab in the 2nd or 3rd trimester has been associated with the potential for transient B-cell depletion in the neonate in small case series (33). It is therefore recommended to avoid live vaccinations of infants

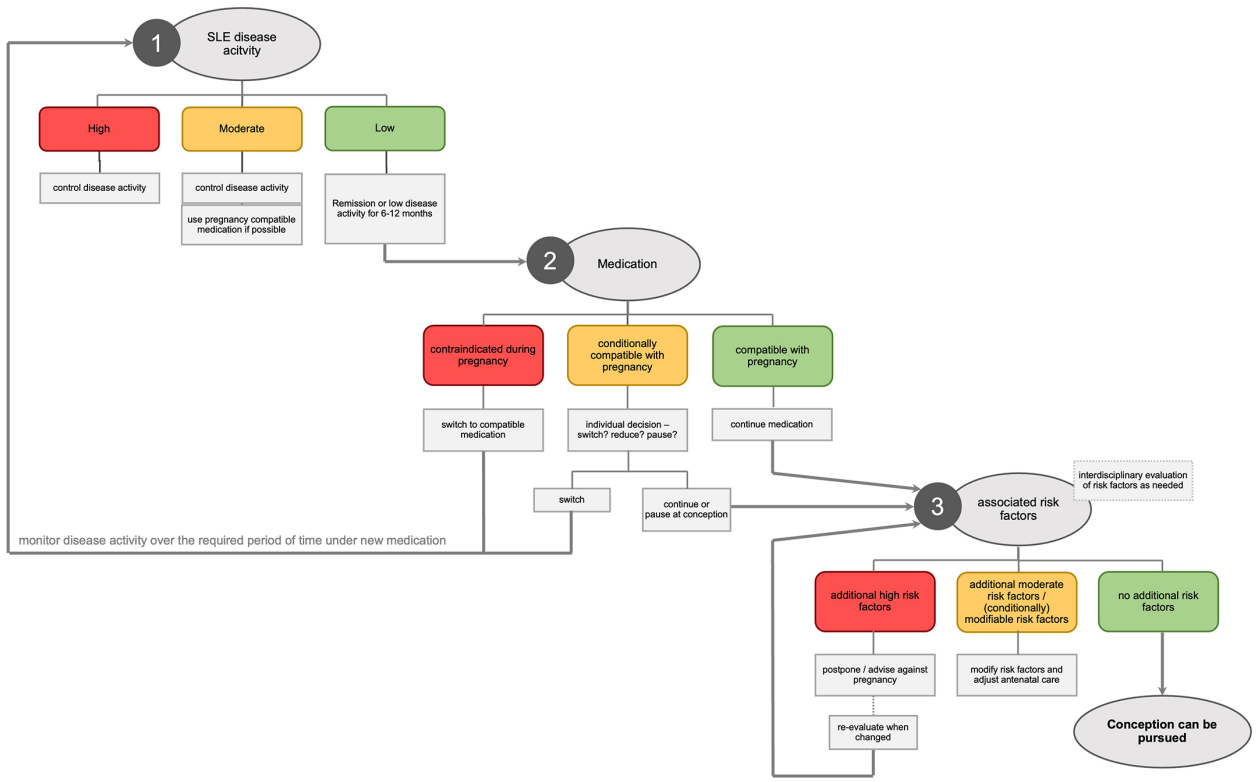

FIGURE 1
Proposed algorithm to plan pregnancy in SLE and APS patients.

if the mother has been treated from the 2nd trimester onwards with one of these biologics.

For drugs with known teratogenic effects (namely cyclophosphamide, mycophenolate mofetil and methotrexate), discontinuation before conception is advised, with the usual recommendation being that compatible alternatives be employed. The effectiveness and tolerability of the new treatment should be assessed for at least 3–6 months before attempting pregnancy.

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers are often used in the management of lupus nephritis or hypertension. Exposure during the 2nd and 3rd trimesters can result in inadequate blood supply to the placenta, leading to fetal hypotension, renal impairment, and oligohydramnios (34, 35). In line with current recommendations, the most practical approach is to cease these medications at the time of a positive pregnancy test and, if necessary, employ safe alternatives, such as methyldopa (36). SGLT2 inhibitors are increasingly used due to their nephroprotective features. *in vitro* studies suggest placental transfer and the available data on SGLT2 inhibitors in human pregnancy is very scarce and insufficient to allow the formulation of any recommendations regarding their use (37, 38).

Phenprocoumon and Warfarin are associated with an increased risk of major malformations if the unborn child is exposed at 9th gestational week (GW) or later and is replaced by therapeutic low-molecular-weight heparin (LMWH) (39). In clinical practice, this change is justifiable in the case of a positive pregnancy test up to the 6th week of pregnancy if a regular menstrual cycle, comprehensive information and adherence are given.

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used until the 28th week at the lowest effective dose, when risk of premature closure of the ductus arteriosus botalli increases, but their use should be restricted from the 20th week due to potential renal dysfunction and oligohydramnios (40). In contrast, low-dose acetylsalicylic acid (LDA) is safe and demonstrated reduction of pre-eclampsia risk if started before 16th GW (41). Hence, it is recommended for all women with SLE, particularly if additional risk factors are present (e.g., extreme age, arterial hypertension, pre-existing renal disease or aPL).

4.3 Step 3: assessment of associated risk factors

Although often overlooked, the assessment of associated risk factors is an element as important as the evaluation of disease activity and the adjustment of medication. These can be broadly divided into three categories: Factors directly related with SLE (severe organ manifestations or damage, and some autoantibodies that pose additional risk), maternal risk factors and comorbidities, and previous pregnancy complications. Table 1 provides a comprehensive overview of the key considerations.

Basic measures include advising all women planning a pregnancy to take daily folic acid and ensure adequate vitamin D intake, particularly if heparin or glucocorticoids (GCs) are employed. It is also highly recommended that vaccination status is up to date.

While most additional risk factors can be managed effectively, there are instances where pregnancy is contraindicated. This is particularly true in cases of severe cardiac, pulmonary, or renal impairment, or when previous severe pregnancy complications occurred despite appropriate treatment (27).

4.4 Digression: neonatal lupus

The presence of anti-Ro/SS-A and anti-La/SS-B antibodies can lead to neonatal lupus, which manifests in two forms that differ in timing and severity. About 10% of neonates may experience transient, self-limiting postnatal symptoms, such as annular erythematous lesions, asymptomatic liver involvement,

TABLE 1 Assessment of additional risk factors in SLE pregnancies.

Risk stratification additional risk factors				
	Organ manifestations	**Laboratory parameters**	**Previous pregnancy complications**	**Maternal risk factors & comorbidities**
Contraindication for pregnancy	• Irreversible severe organ damage with relevant functional impairment		• Previous severe pregnancy complication	
Modify where possible & adapt follow-up	• Cardiac manifestation • Pulmonary manifestation • Renal manifestation	• aPL (risk profile) • Anti-Ro/SS-A anti-La/SS-B	• Miscarriages • Fetal death • IUGR • (pre-)eclampsia • HELLP syndrome • Preterm birth • SGA infant	• Age • Obesity • Arterial hypertension • Diabetes mellitus • Thyroid disease • Previous thrombosis or non-modifiable risk factors for thrombosis • (incomplete) vaccination status • Alcohol • Nicotine

mild hepatosplenomegaly, and cytopenia. More concerning is the risk o congenital heart block (CHB), which may develop between the 18th and 26th GW in 1%–2% of cases, with a recurrence risk of approximately 17% in subsequent pregnancies (42–44). For women with a previously affected fetus, weekly fetal echocardiograms are recommended from 16th GW to monitor for CHB. In women with no prior history of CHB, the optimal frequency of monitoring is debated, with suggestions ranging from biweekly checks to checks during routine obstetric visits, largely due to the fact that there is no effective treatment if CHB is detected (45). Fluorinated GCs and IVIG have shown no better efficacy than a wait-and-see strategy (46, 47). HCQ is currently the only medication proven to reduce the risk of CHB when started before conception or early in pregnancy (48, 49).

4.5 Digression: aPL and APS

According to EULAR and ACR recommendations, women with SLE and high-risk aPL profile (LA positive or double/triple positive for aPL) without previous thrombotic or obstetric manifestations should receive LDA during pregnancy. If a history of obstetric APS is present, LDA should be initiated prior to conception and supplemented with prophylactic LMWH as soon as the pregnancy test is positive until 6–12 weeks postpartum. In the case of thrombotic APS, LDA should be started upon pregnancy in addition to therapeutic LMWH. In refractory cases despite these measurements, escalation from prophylactic to therapeutic LMWH or addition of HCQ or low-dose prednisolone can be considered on a case-by-case basis (27, 50).

4.6 Final remarks: individualized risk stratification and tailored treatment plan

Considering disease activity, medication and additional risk factors, an individualized risk stratification is carried out step by step with a special attention to modifiable risks. Based on this assessment, patient and physician can collaboratively set up a tailored treatment plan with necessary measures before and during pregnancy. This also sets the starting point to build a multidisciplinary team with obstetricians and others to monitor and manage the pregnancy closely. Of course, frequent adjustments to the treatment plan might be made as pregnancy progresses.

5 Discussion

Pregnancy in women with SLE and APS requires meticulous planning and management to mitigate risks and improve outcomes. By leveraging current knowledge and available treatments, rheumatologists can support these patients in achieving successful pregnancies. However, major challenges remain, and ongoing research is promising to address these.

5.1 Neonatal lupus

Up until this point in time, it has not been possible to provide women with anti-Ro/SS-A and anti-La/SS-B antibodies with a more accurate estimation of the actual risk of their offspring developing CHB than the figures previously mentioned. This impairs optimized and cost-effective monitoring and therapeutic approaches. The STOP BLOQ study examines a multi-step approach to address various obstacles simultaneously. The initial findings of this ongoing study appear to corroborate the hypothesis that elevated anti-Ro/SS-A titers are associated with an increased prevalence of CHB, and that low titers may possess a potential negative predictive value. Moreover, the authors present compelling evidence for the efficacy of home monitoring conducted by expectant women for the prompt identification of newly emerging CHB (51). The hypothesis that this early detection of CHB in a population at higher risk provides a window of opportunity for therapeutic intervention is now being investigated.

5.2 Therapeutic options in APS

The protective role of HCQ in the context of pregnancy is well established in SLE. However, its potential benefit in the context of APS is less clear. Retrospective cohort studies suggest that the addition of HCQ to standard treatment in refractory obstetric APS is associated with fewer miscarriages, a higher live birth rate and a lower prevalence of pre-eclampsia and IUGR (52, 53).

However, the validity of these studies is limited due to their retrospective nature, heterogeneous groups and small cohort size. Given the potential benefit of this long-known, pregnancy-compatible and well-tolerated substance in refractory high-risk pregnancies, there is an urgent need for more reliable data. Accordingly, the HYPATIA study, a prospective, randomized, controlled trial designed to address this question, is highly commended.

Another promising avenue for improving pregnancy outcomes of women with APS is the IMPACT study. The authors have previously identified TNF-α as a critical downstream effector of abnormal placental development in APS, which can lead to fetal damage, pre-eclampsia and placental insufficiency (54). They are now investigating the potential protective effect of certolizumab in relation to APOs associated with poor placentation. Preliminary results indicate safety even with respect to the development of anti-dsDNA-antibodies or signs of SLE (55).

5.3 Future directions

These studies, along with other ambitious and outstanding projects, will enhance our understanding and broaden our

diagnostic and therapeutic armamentarium. This will inform updates to the guidelines and eventually improve the care and counselling provided to women with SLE and APS.

Author contributions

IH: Visualization, Writing – original draft. RF-B: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Monoclonal antibodies targeting type 2 inflammation in eosinophil-associated diseases during pregnancy: insights from two eosinophilic granulomatosis with polyangiitis cases and a comprehensive literature review

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Background: With the widespread availability of monoclonal antibodies targeting type 2 inflammation, managing pregnancies in patients with eosinophil-associated diseases, including eosinophilic granulomatosis with polyangiitis (EGPA), has become a crucial issue.
Methods: Starting from a two-case series of patients with EGPA, safely treated with anti-interleukin (IL)5/IL5R monoclonal antibodies during pregnancy, we conducted a comprehensive literature review to identify cases reporting the use of monoclonal antibodies for treating EGPA and other eosinophil-associated diseases in pregnant women.
Results: We present two cases of patients with ANCA-negative EGPA. The first case involves a 35-year-old patient with benralizumab, resulting in successful disease control and a healthy pregnancy despite a history of miscarriage and gestational diabetes. The second case describes a 35-year-old woman who continued mepolizumab during pregnancy, leading to a healthy infant despite two prior early miscarriages. A literature review of 22 papers, covering 97 patients using biologics during pregnancy found no reports specific to EGPA but documented safe outcomes with monoclonal antibodies like mepolizumab, benralizumab, and dupilumab in other eosinophil-associated disorders. These biologics were effective in managing symptoms and reducing the need for oral glucocorticoids, with no observed teratogenic effects. However, complications such as gestational diabetes and preterm births were noted, particularly with dupilumab. No adverse events or pregnancy complications directly attributable to the biological therapy were reported.
Conclusions: Uncontrolled disease during pregnancy significantly threatens pregnancy viability, while the use of monoclonal antibodies effectively manages maternal disease, reduces glucocorticoid use, and helps prevent complications, even though more data are needed to establish risks and benefits.

KEYWORDS

EGPA, pregnancy, mepolizumab, dupilumab, benralizumab, vasculitis, conception, breastfeeding

1 Introduction

Over the past two decades, a range of inflammatory diseases affecting multiple organ systems and characterized by elevated eosinophil counts have been described and characterized. These eosinophil-associated diseases include common conditions such as asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and atopic dermatitis (AD), less common eosinophilic gastrointestinal diseases, and rare conditions such as allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA), and hypereosinophilic syndromes (HES) (1).

EGPA is a rare, potentially life-threatening autoimmune vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA). It is characterized by necrotizing vasculitis of small vessels, eosinophil-rich granulomatous inflammation, and elevated blood eosinophils. EGPA typically presents between the 5th and 6th decades of life but can also affect women of childbearing age (2). Treating EGPA is challenging due to its rarity, broad clinical manifestations, and similarities with other vasculitic or eosinophilic conditions. The primary treatment is systemic glucocorticoids (GCs), often combined with immunosuppressive agents depending on disease severity and the organs involved (3).

Monoclonal antibodies targeting type 2 inflammation have proven effective in treating eosinophil-associated diseases, especially when conventional treatments are ineffective or poorly tolerated. Initially approved for asthma, these therapies are now also approved for chronic spontaneous urticaria, AD, EGPA, CRSwNP, and HES. Currently, seven biologics, namely omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab, and tralokinumab, are approved for these conditions (4, 5). Nevertheless, the randomized clinical trials that led to Food and Drug Administration (FDA) approval frequently excluded pregnant women, thereby leaving the safety and efficacy of these biologics during pregnancy largely unknown.

Managing pregnancies in patients with eosinophil-associated diseases requires a careful risk-benefit assessment. This due to the potential exacerbation of eosinophilic and atopic conditions, which can lead to unfavorable pregnancy outcomes, and limited availability of drugs during this period (6–8).

In this paper, we present a two-case series of patients with EGPA who were safely treated with anti-interleukin (IL)5/IL5R monoclonal antibodies during pregnancy. Additionally, we provide a comprehensive review of the available English-language literature on the use of biologics targeting type 2 inflammation during pregnancy in eosinophil-associated disorders, focusing on their safety concerning maternal and fetal outcomes.

2 Methods

Starting from clinical cases of two patients with long-standing EGPA in regular follow-up at the Padua Vasculitis Center, successfully treated with anti-IL5/R during pregnancy, we conducted an extensive literature search in MEDLINE via PubMed for original articles published up to July 15, 2024, reporting on the use of monoclonal antibodies to treat EGPA and other eosinophil-associated diseases in pregnant women. The search utilized the following MeSH terms: "eosinophilic granulomatosis with polyangiitis", "EGPA", "Churg-Strauss syndrome", "hypereosinophilic syndrome", "HES", "severe asthma", "chronic sinusitis with nasal polyps", "atopic dermatitis", "eosinophilic esophagitis", "Benralizumab", "Dupilumab", "Mepolizumab", "Reslizumab", "Tezepelumab", "Tralokinumab", "pregnancy", "post-partum", and "breastfeeding".

Omalizumab was excluded from the review due to established safety data in pregnancy from the Xolair Pregnancy Registry (EXPECT) study on severe asthma (9). The EXPECT study, the largest prospective study on omalizumab use during pregnancy, found similar rates of live births and major congenital malformations in 230 pregnant women with asthma exposed to omalizumab compared to a matched external cohort.

For each publication, we focused on clinical findings, treatment management, and maternal and fetal outcomes. We excluded studies where biologics were used after delivery to treat relapses or worsening of the diseases, as well as studies where biologics were discontinued before conception or where the treatment involved the father instead of the mother.

Statistical analysis was performed using the free software Jamovi (version 1.6.15). Medians and interquartile range were calculated for continuous variables, while percentages and relative frequency distributions were used for categorical variables. Analyses were conducted only on subjects with available data.

All patients signed informed consent forms, and this study was conducted in accordance with the Ethical Principles for Medical Research outlined in the Declaration of Helsinki.

3 Results

3.1 Case description

3.1.1 Case 1

The first case involves a 35-years-old patient diagnosed with ANCA-negative EGPA in 2018, fulfilling the 2022 ACR/EULAR classification criteria for EGPA (10). At the time of diagnosis, she presented with hypereosinophilia (blood eosinophil count of 15,000/mmc), pulmonary infiltrates, systemic symptoms, and skin purpura, along with a history of severe asthma and chronic sinusitis with nasal polyposis. Initially, she was treated with GCs, methotrexate up to 15 mg/week, followed by mepolizumab 100 mg/4 weeks (as the 300 mg/4 weeks dose was not approved at that time), but asthma control was not achieved. Subsequently, she was administered benralizumab 30 mg every 8 weeks for a period of two years in order to control her uncontrolled asthma. This resulted in the successful cessation of oral GCs after six years of continuous treatment, and the achievement of disease remission. The patient had no history of smoking, was overweight with a body mass index (BMI) of 36, and tested positive for lupus anticoagulant. While on benralizumab, she experienced a miscarriage at 7 weeks of gestation. However, she

subsequently became pregnant again and continued benralizumab treatment alongside antiplatelet therapy. Benralizumab was discontinued at the end of the second trimester, and the patient refrained from further benralizumab treatment throughout breastfeeding. The pregnancy was complicated by gestational diabetes, which required insulin treatment, and ended in a cesarean delivery at 40 weeks of gestation. No vasculitic relapses, asthma exacerbations, or increases in eosinophil levels were observed. The infant was born healthy. During breastfeeding, the mother received a short course of oral GCs due to an asthma exacerbation accompanied by a transient increase in blood eosinophils (2,300/mmc) and C-reactive protein (17 mg/L).

3.1.2 Case 2

The second case involves a 36-years-old patient diagnosed with ANCA-negative EGPA, fulfilling the 2022 ACR/EULAR classification criteria for EGPA (10). She had a history of adult-onset asthma, chronic rhinosinusitis with nasal polyps, systemic symptoms, myocarditis and serositis. Initially, she was treated with high-dose GCs combined with cyclophosphamide, followed by azathioprine and oral GCs for 6 years Due to uncontrolled asthma and persistent eosinophilia (blood eosinophil count above 1,000/mmc), she was switched to mepolizumab 300 mg every 4 weeks. The patient was a former smoker and had previously undergone a cesarean delivery in a prior pregnancy. While receiving mepolizumab, the patient experienced two early spontaneous miscarriages at 6 weeks of gestation. However, during a subsequent pregnancy, which occurred one year after starting the biologic, she continued mepolizumab until the end of the second trimester (25 weeks of gestation). The pregnancy proceeded without complications, resulting in the birth of a healthy infant via cesarean delivery at 38 weeks of gestation. Throughout her pregnancy, the patient did not experience any adverse events, hypereosinophilia, or disease relapse. However, during the postpartum period, her asthma symptoms worsened and were not adequately managed by combination inhalers. These symptoms were effectively controlled with the resumption of mepolizumab at a dosage of 300 mg every GC weeks.

Clinical features, blood tests and patient-reported outcome measures of the two EGPA cases during conception, pregnancy and post-partum are listed in Table 1.

3.2 Literature review

A total of 22 papers documenting the use of biologics in eosinophil-associated diseases during pregnancy, encompassing 97 patients, were retrieved from the published literature (11–32). These include mostly case reports, along with four case series (11, 15, 25, 30), one longitudinal study (27) and one retrospective cohort study (32).

No reports were found for EGPA patients treated with monoclonal antibodies targeting type 2 inflammation during pregnancy. Monoclonal antibodies were used, continued or started when disease control was lost before or during pregnancy and other therapeutic options were unavailable. Most patients had only partial responses to standard therapies or encountered issues with immunosuppressants (20) or infections (16, 25). Table 2 provides a summary of maternal and neonatal outcomes following exposure to biologic therapies at different stages of pregnancy. Table 3 presents a summary of all cases retrieved from the literature review, including our two EGPA cases, detailing demographic and clinical features, timing of biologic exposure, and maternal and neonatal outcomes in patients with eosinophil-associated diseases treated with biologic therapies.

The median duration of therapies before conception could not be calculated due to insufficient data, and information on the duration of treatment in terms of gestational weeks was often unavailable. However, Figure 1 illustrates the proportion of patients exposed to mepolizumab, benralizumab, and dupilumab during various stages of pregnancy, including conception, the first, second, and third trimesters, and breastfeeding.

TABLE 1 Blood tests, disease activity and damage scores of the two patients treated with anti-IL5/5R monoclonal antibodies at different stages of pregnancy.

	Before pregnancy	During pregnancy	Post partum	Breastfeeding
Case 1 (benralizumab 30 mg every 8 weeks)				
Eosinophils (cell/mmc)	0	20	0	2,300
CRP (mg/L)	7.5	4.9	–	17
BVASv3	0	0	0	2
VDI	3	3	3	3
ACT	23	21	25	17
Oral GC use	No	No	No	Yes
Case 2 (mepolizumab 300 mg every 4 weeks)				
Eosinophils (cell/mmc)	100	0	300	–
CRP (mg/L)	0.5	0.6	0.4	–
BVASv3	0	0	2	0
VDI	3	3	3	3
ACT	21	21	18	25
Oral GC use	No	No	No	No

ACT, asthma control test; BVASv3, Birmingham vasculitis activity score version 3; CRP, C-reactive protein; GC, glucocorticoid; VDI, vascular damage index.

TABLE 2 Maternal and neonatal outcomes following exposure to mepolizumab, benralizumab, and dupilumab during different stages of pregnancy.

	Mepolizumab (*n* = 6)	Benralizumab (*n* = 8)	Dupilumab (*n* = 88)
Disease (n. of patients)	SA (3), EGPA (1)	SA (5), HES (1), EGPA (1)	AD (84), PG (4)
Efficacy of biologics and maternal outcomes			
Patients treated with GC before biologics, *n*	1 EGPA, 2 SA	1 EGPA, 5 SA	28/30 (AD)
GC reduction/discontinuation, *n*	–	1/1	4/5 (3 PG, 1 AD)
Relapses with biologics, *n*	1/4	2/7	1/88
Relapses without biologics, *n*	2/4	1/7	4/88
Pregnancy and neonatal outcomes			
Numbers of deliveries, *n*	3/5 (2 miscarriages)	6/7 (1 miscarriage)	55/60 (5 miscarriages)[a]
Pregnancy complications, *n*	0/3	1/6	7/55
Neonatal complications, *n*	0/3	0/6	13/60

AD, atopic dermatitis; EGPA, Eosinophilic Granulomatosis with Polyangiitis; GC, glucocorticoids; HES, hypereosinophilic syndrome; PG, pemphigoid gestations; SA, severe asthma.
[a]1 twin couple.

Globally, no teratogenic effects were observed, and all infants were healthy at birth and during the observation period.

3.2.1 Mepolizumab

A total of three pregnant patients with chronic asthma were treated with mepolizumab 100 mg every 4 weeks (11, 12). All patients were exposed to the drug at conception and during the first trimester (11, 12). Only one patient continued treatment into the third trimester and during breastfeeding (12). One pregnancy was voluntarily terminated during the first trimester due to concerns about drug's potential unknown effects (11). No adverse events or pregnancy complications were reported, except for the voluntary abortion mentioned above (11). The efficacy of the drug in controlling the disease exhibited considerable variability. One patient experienced a relapse after discontinuing the drug in the second trimester (11), while another patient achieved only partial asthma control, with two relapses during treatment (12). Two patients had previously received oral GCs but were not using them at the time of conception. Both patients who experienced relapses required a short course of oral GCs (11, 12). No further details on the timing and dosage are of oral GCs available in the published literature.

3.2.2 Benralizumab

Six pregnant patients, comprising five patients with chronic asthma (13, 15) and one with HES (14), were treated with benralizumab 30 mg every 8 weeks. Five patients were exposed to the drug at conception (13–15), and four continued into the first trimester (14, 15). Six were exposed to the drug during the second trimester (13–15). Five patients continued treatment through the third trimester (14, 15), and three infants were breastfed while their mothers were receiving benralizumab (15). Two patients experienced asthma attacks during treatment, but other risk factors, such as smoking habits and poor adherence to topical treatment, were also reported (15). No pregnancy complications occurred. Blood eosinophils were measured in two infants and were undetectable for several weeks, with no observed developmental or immune system issues (14, 15). Five patients had previously received oral GCs (13–15). Only one patient was using GCs when starting benralizumab and was able to reduce the dosage during the pregnancy (13).

3.2.3 Dupilumab

A total of 88 pregnant patients were identified, including 84 patients with AD (16–19, 21–23, 25, 27, 28, 30–32) and four with pemphigoid gestationis (PG) (20, 24, 26, 29) treated with dupilumab. Among these, 74 out of 84 patients with AD (17–19, 21–23, 25, 27, 28, 30–32) were exposed to the drug at conception, while none of the patients with PG were exposed at conception. In the first trimester, 74 patients continued treatment (17–19, 21–23, 25, 27, 28, 31, 32), decreasing to 30 in the second trimester (17–19, 21–23, 25, 27–31) and 31 in the third trimester (16–18, 20–31). 15 infants were breastfed while their mothers were on dupilumab (16–18, 25, 28, 31).

Dupilumab generally controlled disease activity, though one patient (1.1%) with AD experienced a flare during treatment and shortly after the delivery (16). Additionally, four (4.5%) patients with AD relapsed after discontinuing dupilumab, with relapses occurring in both the first (30) and third trimesters (19, 22, 30). All patients with PG achieved disease control and remission (20, 24, 26, 29).

Pregnancy complications were reported, including three cases of gestational diabetes (16, 19, 32), two cases of oligohydramnios (32), one case of postpartum hemorrhage (32), five miscarriages (32) in AD, and one case of premature rupture of membranes in PG (20). Of the three cases of gestational diabetes, two occurred in patients receiving GC treatment, and one occurred in a patient not treated with GC. Additionally, there were 11 preterm births (20, 25, 26, 32), one infant with respiratory distress and one infant with pulmonary hypertension (32). Most pregnancy and neonatal complications occurred in cases where dupilumab was discontinued before the third trimester. Of the 7 pregnancy complications, 5 occurred in these cases. Similarly, 9 out of 11 neonatal complications (after excluding 2 cases with missing data

TABLE 3 Demographic and clinical features, timing of biologic exposure, maternal and neonatal outcomes in patients with eosinophil-associated diseases treated with biologic therapies.

Author, year	Disease	Age at disease onset, y	Age at pregnancy, y	Previous pregnancies and complications	Biologic exposure before pregnancy, m	Timing of biologic exposure	Maternal outcomes	Pregnancy complications	Neonatal outcomes
Mepolizumab ($n = 4$)									
Ozden, 2021 (11)	SA	20	25	0	1	Conception, 1T	Disease remission, 2 relapses after drug discontinuation requiring GC	No	Healthy infant
	SA	30	36	3	1	Conception, 1T	Disease remission	–	Voluntary abortion
Vittorakis, 2023 (12)	SA	16	26	0	4	Conception, 1 T, 2 T, 3 T, breastfeeding	Partial remission, 2 relapses requiring GC	No	Healthy infant by CD
Present case	EGPA	25	36	1	12	Conception, 1 T, 2 T	Disease remission, 1 post-partum relapse	No	Healthy infant by CD, 2 miscarriages (6th gw)
Benralizumab ($n = 7$)									
Saco, 2018 (13)	SA	–	31	–	–	Conception, 2T	Disease remission, GC reduction	–	–
Manetz, 2021 (14)	HES	22	36	–	–	Conception, 1 T, 2 T, 3T	Disease remission	No	Healthy infant by CD, Eosinophil depletion for 7 months
Naftel, 2023 (15)	SA with CRS	27	29	3, 1 GD	24	Conception, 1 T, 2 T, 3 T, breastfeeding	Disease remission	No	Healthy infant by CD, Eosinophil depletion for 7 weeks
	SA with CRS	10	29	4, 1 abortion	1	Conception, 1 T, 2 T, 3 T, breastfeeding	Partial remission, 2 relapses	No	Healthy infant
	SA with CRS	Lifelong history	23	0	12	Conception, 1 T, 2 T, 3T	Partial remission, 4 relapses	No	Healthy infant
	SA with CRS	22	27	3, 1 abortion	–	2 T, 3 T, breastfeeding	Disease remission	No	Healthy infant by CD
Present case	EGPA	31	34	1	24	Conception, 1T	Partial remission, 1 post-partum relapse requiring GC	GD	Healthy infant by CD, 1 miscarriage (7th gw)
Dupilumab ($n = 88$)									
Mian, 2020 (16)	AD	Lifelong history	28	2	–	3 T, breastfeeding	Partial remission, 1 post-partum relapse, GC discontinuation	GD	Healthy infant
Kage, 2020 (17)	AD with allergic asthma	Lifelong history	35	0	8	Conception, 1 T, 3 T, breastfeeding	Disease remission	No	Healthy infant
Kage, 2021 (18)	AD with allergic asthma	Lifelong history	36	1	24	Conception, 1 T, 2 T, 3 T, breastfeeding	Disease remission	No	Healthy infant
Lobo, 2021 (19)	AD with asthma	Lifelong history	36	1	12	Conception, 1 T, 2T	Disease remission, 1 relapse after drug cessation	GD	Healthy infant

(*Continued*)

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TABLE 3 Continued

Author, year	Disease	Age at disease onset, y	Age at pregnancy, y	Previous pregnancies and complications	Biologic exposure before pregnancy, m	Timing of biologic exposure	Maternal outcomes	Pregnancy complications	Neonatal outcomes
Riquelme- Mc Loughlin 2021 (20)	PG	–	37	5, 1 abortion, 1 PG	–	3 T	Disease remission	Premature rupture of membranes	Healthy preterm infant (34th gw) by CD
Gracia-Darder, 2022 (21)	AD, hyper IgE syndrome, ulcerative colitis, asthma	10	28	0	10	Conception, 1 T, 2 T, 3 T	Disease remission	No	Healthy infant
Akhtar, 2022 (22)	AD	Lifelong history	33	1	12	Conception, 1 T, 2 T, 3T	Disease remission, 1 relapse during drug discontinuation	No	Healthy infant by CD
Costley and Murphy, 2022 (23)	AD	Lifelong history	–	–	Several months	Conception, 1 T, 2 T, 3T	Disease remission	No	Healthy infant
Alvarez Martinez, 2023 (24)	PG	–	28	–	–	3 T, up to 6 weeks postpartum	Disease remission, GC discontinuation	No	Healthy infant
Escolà, 2023 (25) (*N* = 13)	AD	30 (16–39)	33 (28–41)	–	Before pregnancy (9)	Conception (9), 1 T (9), 2 T (8), 3 T (8), breastfeeding (10)	–	No	12 healthy infants, 1 twin preterm (35th gw) pregnancy by CD
Liu, 2023 (26)	PG	–	28	2, 2 abortions	–	3T	Disease remission, GC reduction	–	Healthy preterm infant (36th gw) by CD
Schoder, 2023 (27) (*N* = 29)	AD	–	–	–	–	Conception (25), 1T (25), 2 T (11), 3 T (11)	–	–	–
Alvarenga, 2023 (28)	AD	0	37	–	36	Conception, 1 T, 2 T, 3 T, breastfeeding	Disease remission	No	Healthy infant
Chen, 2023 (29)	PG	–	36	1 PG	–	2 T, 3 T, after delivery	Disease remission, GC discontinuation	No	Healthy infant
Hong, 2024 (30) (*N* = 4)	AD	–	33, 35, 39, 29	–	–	Conception (3), 2 T (3), 3 T (1)	Disease remission, 2 relapses	No	Healthy infants
Di Lernia, 2024 (31)	AD	Lifelong history	35	0	24	Conception, 1 T, 2 T, 3 T, breastfeeding	–	No	Healthy infant
Avallone, 2024 (32) (*N* = 29)	AD	–	30 (19–45)	2 pregnancy loss, 2 adverse events	22.5 weeks (IQR 3-118)	Conception, 1 T and 2 T	Disease remission, 1 GC course	1 GD, 1 PPH, 2 oligohydramnios	Healthy infants, 5 miscarriages, 7 prematurity, 1 respiratory distress, 1 pulmonary hypertension

1T, first trimester; 2T, second trimester; 3T, third trimester; AD, atopic dermatitis; CD, cesarean delivery; CRS, chronic rhinosinusitis; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoids; GD, gestational diabetes; HES, hypereosinophilic syndrome; IgE, immunoglobulin E; IUGR, intrauterine growth restriction; PG, pemphigoid gestationis; PPH, post-partum hemorrhage; SA, severe asthma.

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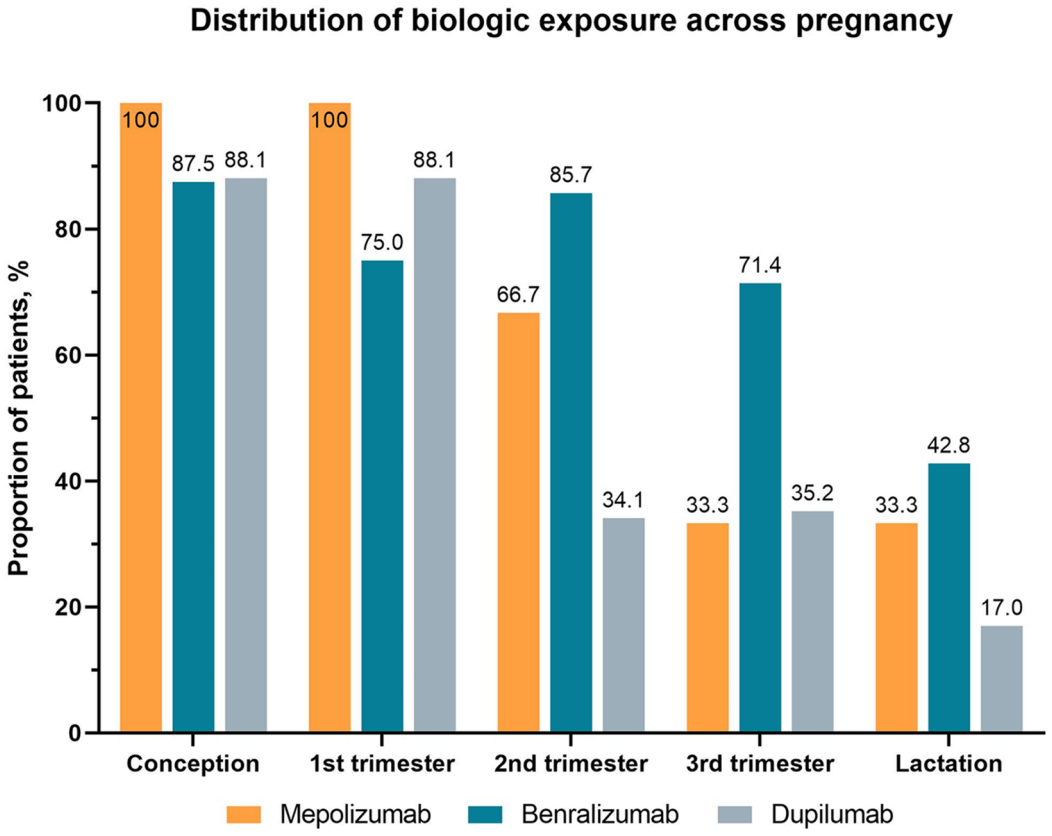

FIGURE 1
Proportion of patients receiving mepolizumab, benralizumab and dupilumab across different stages of pregnancy and lactation.

from a total of 13) were associated with early discontinuation of dupilumab. Despite these complications, no teratogenic effects were observed, and all infants were healthy at birth and during the observation period.

Regarding GCs, 28 out of 30 patients had previously received GC treatment, while no data on prior GC use were available for the remaining 58 patients. Of the 28 patients, only five were undergoing GC therapy at the start of dupilumab treatment (16, 20, 24, 26, 29). Four of these patients were able to reduce or discontinue GCs during pregnancy (16, 24, 26, 29). Finally, one patient who had not previously been treated with GCs required a short course of GCs to control AD symptoms (32).

3.2.4 Reslizumab, tezepelumab and tralokinumab

There are no published human data on the use of reslizumab, tezepelumab, or tralokinumab during pregnancy, making the potential risks to maternal and fetal outcomes unknown. Animal studies in mice, rabbits, and monkeys exposed to these drugs at higher doses have shown no evidence of embryo-fetal developmental harm (33–35). However, the absence of human data leaves the safety of these treatments during pregnancy uncertain.

4 Discussion

To the best of our knowledge, the clinical cases described in this paper are the first published reports of managing EGPA in pregnancy with benralizumab or mepolizumab. Both patients had relapsing, refractory EGPA and responded well to biologic therapy, without the use of oral glucocorticoids during pregnancy. There were no adverse events or relapses, although the treatments were stopped in the third trimester. Both pregnancies ended in cesarean sections with healthy neonates. While both patients experienced miscarriages during treatment, a direct link to the biologics could not be established due to the presence of additional risk factors such as advanced maternal age and autoimmune diseases. Moreover, in the patient treated with benralizumab, the complication of gestational diabetes was associated with other risk factors, such as maternal age and overweight. In both of our patients, other potential predictors of miscarriage were excluded.

The patients presented in this paper underscore the challenges of managing pregnancy in patients with EGPA and eosinophil-associated diseases. A major concern is the limited availability of safe medications during this period. Most immunosuppressive drugs, except azathioprine and cyclosporine, are contraindicated during pregnancy (36). Additionally, glucocorticoids, a

cornerstone of treatment for eosinophil-mediated diseases, carry gestational risks, including gestational diabetes, stillbirth, preterm birth, low birth weight, and cesarean delivery (37). Optimizing medical management for these patients is crucial, but current data and guidelines are insufficient for routine clinical practice.

The widespread use of monoclonal antibodies targeting type 2 inflammation in eosinophil-associated conditions raises concerns about their safety during pregnancy, given the limited data available. Pregnant or breastfeeding women, or those planning conception, are typically excluded from clinical trials, leaving safety assessments reliant on case reports, animal studies, small retrospective studies, or pregnancy registries, which may be biased and lack consistent medication adherence.

Current literature indicates that many patients discontinue monoclonal antibody therapy in the third trimester due to concerns about transplacental transfer and persistence in breast milk. Immunoglobulins are transported across the placenta in a linear fashion as pregnancy progresses (38), aligning with the development of the fetal Fc receptor for immunoglobulin G (IgG) (39–41). While IgG can be transferred through breast milk, its secretion and absorption are limited to the first few days of life and in preterm infants with immature gastrointestinal tracts (42, 43). Preclinical studies indicate that benralizumab and mepolizumab cross the placenta in the third trimester, with mepolizumab present in breast milk at less than 0.5% of maternal serum concentration (44).

No adverse fetal effects have been observed with any of the treatments. In cases where benralizumab and mepolizumab were continued throughout pregnancy, no complications were reported, and full-term healthy infants were delivered. The absence of eosinophils in two infants exposed to benralizumab until birth was not linked to developmental or immune issues, although long-term effects remain unclear (14, 15). Eosinophil suppression in mice also shows no associated developmental problems (45). Data on dupilumab suggests that complications mainly occur when the drug is discontinued before the third trimester, though most infants were born healthy. Additionally, there are concerns that inhibiting IL-13, which promotes mucus-secreting goblet cell proliferation, might impact fetal conjunctival development (27, 46–48), particularly before the third trimester when these cells mature (49, 50). However, no infants exposed to dupilumab exhibited any eye-related developmental issues. Moreover, aside from a single reported case of benralizumab-induced eosinophil depletion in an infant, no safety concerns have been identified in breastfed infants. Overall, the available data suggest that biologics are unlikely to have a significant impact on pregnancy or fetal outcomes. However, it is crucial to highlight that data on long-term risks and the potential effects of these drugs on fetal and neonatal development remain uncertain, as follow-up was not reported in many cases.

During pregnancy, the immune system shifts from cell-mediated immunity (type 1 inflammation) to humoral immunity (type 2 inflammation) to maintain immunotolerance and prevent fetal rejection (51). However, this immunological shift can also trigger, exacerbate, or worsen underlying autoimmune or eosinophilic conditions. Some observational studies have explored the outcomes of patients affected with systemic vasculitis during pregnancy (36, 52), with reports of EGPA onset, miscarriage or vasculitis flare, particularly in the first and second trimesters and postpartum (6, 46, 47). Active EGPA is associated with a range of pregnancy complications, including preeclampsia (rare), fetal loss (10%–15%), therapeutic abortion (5%–10%), preterm deliveries (10%–40%), cesarean deliveries (15%–40%), intrauterine growth restriction (10%–25%) and low birth weight infants (10%–30%) (7, 46). Asthma attacks and AD flares also tend to increase during pregnancy (48, 53). Uncontrolled asthma is linked to adverse pregnancy outcomes, including gestational hypertension, diabetes, preeclampsia, premature rupture of membranes, ante- or postpartum hemorrhage, as well as neonatal complications like preterm birth, low birth weight, neonatal death, and congenital malformations (53, 54). Premature rupture of membranes and preterm labor are also complications associated with PG (55), while gestational diabetes is common, particularly with comorbidities and advanced maternal age (56). Although AD itself is not a direct risk factor for adverse pregnancy outcomes, uncontrolled AD can lead to complications like eczema herpeticum, bacterial infections, and reduced quality of life (57–59). In the literature, relapses of asthma and AD have been reported in both treated patients, with some confounding factors as mentioned above, and in untreated patients, particularly after the discontinuation of biologics. However, the use of glucocorticoids during pregnancy, known to carry risks for both mother and infant, has significantly decreased with the introduction of biologics, leading to improved management of the underlying disease.

These data underscore the ongoing risk of disease relapse after biologics discontinuation or following delivery due to immunological shifts. Consequently, uncontrolled disease during pregnancy significantly threatens pregnancy viability, while the use of monoclonal antibodies effectively manages maternal disease, reduces glucocorticoid use, and helps prevent complications. Given that, the 2020 European Respiratory Society/Thoracic Society of Australia and New Zealand (ERS/TSANZ) consider omalizumab probably safe, while mepolizumab, benralizumab, reslizumab, and dupilumab possibly acceptable if conventional therapies fail (60).

We must acknowledge several limitations, primarily related to data heterogeneity, incomplete reporting of maternal and infant outcomes, and the lack of a control group. Additionally, safety information for benralizumab, mepolizumab, and dupilumab in EGPA patients must be inferred from studies in other conditions, thus preventing definitive conclusions. Moreover, the conclusions of this study are constrained by the unavailability of some key predictors, such as maternal age, underlying medical conditions, comorbidities and concomitant drug treatments, which were not reported in the analyzed papers.

In conclusion, our cases, along with the literature review, are encouraging and suggest favorable outcome for monoclonal antibodies targeting type 2 inflammation during pregnancy and breastfeeding. However, more data are needed to establish risks and benefits. These preliminary results can help prevent adverse outcomes that may arise when effective biologic therapy is discontinued due to uncertainty about the medication's effects during pregnancy. They may also aid in the risk-benefit assessment, supporting the decision to continue therapy in

patients who become pregnant unintentionally, based on their individual risk profiles.

Currently, observational studies and industry-sponsored registries evaluating pregnancy outcomes are accumulating evidence for dupilumab in AD and asthma (61–64), mepolizumab in asthma (65, 66) and benralizumab in asthma (67). Although no specific registries exist for monoclonal antibodies in EGPA, the Vasculitis Pregnancy Registry (VPREG) covers all vasculitides (68). Longitudinal studies with adequate follow-up and comparison cohorts are necessary due to the limited number of current cases.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing, Resources, Visualization. LI: Conceptualization, Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing, Resources, Visualization. AC: Investigation, Supervision, Writing – review & editing. AD: Supervision, Validation, Visualization, Writing – review & editing, Funding acquisition. RP: Data curation, Supervision, Validation, Writing – original draft, Writing – review & editing, Funding acquisition, Methodology, Resources, Visualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Motherhood and rheumatic disease – a balancing act. A qualitative study on the challenges of mothers with inflammatory arthritis

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Objective: Inflammatory arthritis (IA) often come with symptoms of pain, stiffness and fatigue, as well as fluctuating and unpredictable disease patterns. All of these symptoms can cause challenges in the role as a mother for women with IA. The main objective of this study is to gain a broader understanding of how mothers with IA experience motherhood and the challenges they encounter within a biopsychosocial framework.

Methods: The participants in this study were recruited through RevNatus, a Norwegian nationwide quality register. The sample consisted of women with IA who had given birth within the last 5 years. The data consisted of written answers to an open-ended question: "Is there anything, in particular, you have experienced as challenging with being a mother and having a rheumatic disease at the same time"? The data were analysed following Brinkmann and Kvale's qualitative content analysis.

Results: 186 women answered the open-ended question. The responses consisted of a total of 9,000 words. Motherhood with IA was described as a difficult balancing act, with practical and physical challenges affecting day-to-day life, medical dilemmas, as well as challenges on a deeper emotional level and worries for the future.

Conclusion: The main finding in this study is that the challenges these women meet are multifactorial and complex, including physical, mental and social issues that have a large impact on their everyday life. Focusing solely on improving medical treatment will not solve the challenges these women face. A multidisciplinary approach and focus on patient education and self-management strategies is important to help these women thrive in their role as mothers with IA.

KEYWORDS

motherhood, rheumatic diseases, arthritis, inflammatory joint disease, women's health

1 Introduction

Inflammatory arthritis (IA) is a term used to describe a heterogeneous group of chronic autoimmune diseases characterised by joint inflammation, such as rheumatoid arthritis, juvenile idiopathic arthritis, spondyloarthritis and psoriatic arthritis (1). Pain, stiffness and fatigue are common symptoms in IA, as well as fluctuating and

unpredictable disease patterns (1, 2). All of these symptoms can cause challenges in the role as a mother for women with IA (3).

Very few women with IA are advised against having children, as we now have more effective treatment and less severe disease manifestations (4). Still, several studies show that IA is associated with higher rates of childlessness, and many women with IA have fewer children than desired (5–8). The reason behind this may be multifaceted with physical, psychological, social, hormonal, immunological, medical and personal challenges contributing (8–10).

The biopsychosocial model, a well-established framework, describes how biological, psychological and social factors interact and affect one another, contributing to a person's experience of his or her overall health (11). This model can help us understand the complexity of living with chronic diseases, such as IA, where biological (e.g., inflammation, sleep deprivation, pain) psychological (e.g., worrying, unpredictability, vulnerability) and social (e.g., living situation, work, family, support) factors dynamically and reciprocally affect one another. In the same way, this model can also be useful to understand the experience of motherhood, regardless of chronic disease, as a multifaceted experience where biological/physical (e.g., physical changes due to pregnancy and labour, sleep deprivation), psychological (e.g., increased vulnerability, expectations) and social (social network, family, work) factors all come in to play.

The vast majority of research on pregnancy and rheumatic diseases focus on medical treatment, risk factors, and pregnancy outcomes. There are some qualitative studies focusing on women's experiences related to pregnancy and the postpartum period, and the number is growing (10, 12–18). The qualitative studies have provided important in-depth insight into how the women experience motherhood while living with IA, and the challenges these women have to cope with. However many of these studies are more than ten years old. There has been a massive development both within the field of rheumatology in general and specifically relating to pregnancy and rheumatic diseases. Access to medical treatment for people with IA, including biologics when indicated is much better than ten-twenty years ago (4, 19, 20).

Having better insight into the possible challenges these women face in their life as mothers with IA can potentially improve patient/clinician communication, and be of great value when developing health services and resources to best support and guide them through this very important part of life.

The aim of this study is thus to gain a broader understanding of how mothers with IA experience motherhood and the challenges they encounter in a biopsychosocial framework.

2 Materials and methods

2.1 Study population

This qualitative study is nested within a larger Norwegian study not yet published, looking at health related quality of life in mothers with IA. Patients were recruited through RevNatus, a nationwide quality register where 17 out of 20 rheumatology departments across Norway contribute with data (21). RevNatus consists of data from women who are 16 years or older with an inflammatory rheumatic disease, who are planning pregnancy or are pregnant. Participants were eligible for this study if they were included in the register and fulfilled the diagnostic- or classification criteria for one of the following diagnosis M05.8, M05.9, M06.0, M07.3+ L40.5, M45, M46.8, M46.9, M08.0 or M08.9, and had registered a live birth within 5 years from 19th of august 2019.

Eligible patients received a letter in the mail with an invitation to participate in the study. After signing an informed consent, the participants answered a questionnaire including an open-ended question aiming to collect in-depth information about perceived challenges related to motherhood and rheumatic disease: "*Is there anything, in particular, you have experienced as challenging with being a mother and having a rheumatic disease at the same time?*".

Age, diagnosis and disease duration were retrieved from RevNatus while educational status, number of children and months since last childbirth were self-reported through the questionnaire.

The data collection found place autumn 2019.

2.2 Data analysis

The responses consisted of a total of 9,000 words and were analysed as described by Brinkmann and Kvale (22). The first, third and last author inductively read and coded all the responses. The research team had several meetings to discuss the content and labels of the codes, during which different interpretations were developed until a consensus of interpretation was reached. The final analytical themes were agreed upon by comparing (finding similarities) and contrasting (searching for negative cases) codes. After reaching an agreement of the main themes, two of the authors went back and read thorough all written responses to see if all important aspects were covered by the themes as agreed upon, in addition to selecting quotes best illustrating the themes.

2.3 Research team

The research team consist of four females (3 MSc and one professor). All are trained nurses with extensive experience within rheumatology. Three out of four are currently working clinically specializing in pregnancy and rheumatic disease.

2.4 Ethics and patient involvement

Participation in the study was voluntary, and all participants signed a written informed consent. The study was approved by REK Sout/East Norway in April 2019 (2019/817/REK sor-ost). Continuous dialogue with two patient representatives have been important during the course of the project.

3 Results

Of the 375 questionnaires sent out, 233 questionnaires were returned, and three letters were returned because of incorrect address, i.e., 62% of eligible subjects responded. 186 of these 233 (80%) answered the open-ended question that this study is based upon. The remaining 47 (20%) left the open-ended question blank and only filled out the questions related to health related quality of life, which is investigated in a separate study.

Table 1 shows the demographic data of the women who responded to the open-ended question. Characteristics of the study population are presented as means and standard deviations or raw numbers and percentages.

3.1 Qualitative findings

The written answers from the open-ended question gave valuable insight to the challenges of motherhood for women with IA. Despite having focus on early diagnosis and good treatment options, mothers with rheumatic disease still describe many challenges related to motherhood.

When analysing the data it became apparent that being a mother with IA is a multifaceted experience. As both motherhood and having an IA diagnosis affects nearly all aspects of these women's lives, they sometimes experienced it as a balancing act. The women described practical and physical challenges that affected their day-to-day life, medical dilemmas, as well as challenges on a deeper emotional level and worries for the future.

One women described it in the following way, summing up many of the challenges these women encompassed, physically and emotionally:

TABLE 1 Characteristics of study population.

Characteristics	*N* = 186
Age (years), mean (SD)	31.9 (4.2)
Number of children *n*, mean (SD)	1.7 (0.7)
Number of months since last childbirth (months), mean (SD)	20.5 (14.3)
Educational status *n* (%)	
Elementary school	3 (1.6)
High school	41 (22)
University/College	142 (76)
Working status *n* (%)	
Working (full/part time)	105 (56)
Not working due to health issues	24 (13)
Not working, other reason	6 (3.2)
Student	9 (5)
Maternity leave	35 (19)
Other	7 (3.8)
Disease *n* (%)	
RA	65 (35)
JIA	27 (15)
AxSpA	69 (37)
PsA	23 (12)
Disease duration (years), mean (SD)	11.7 (7.1)

SD, standard deviation; RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; axSpA, axial spondyloarthritis; PsA, psoriatic arthritis.

> "A lot of things. Where to start? Everything from not being able to breastfeed after giving birth (due to medications) and not being able to take care of the children (holding them, carrying them, picking them up at night). Dad had to take over. Of course it's sad not being able to participate in activities and join them on trips to the extent I want when they're growing up. Many thoughts on their dad. Afraid the kids will look back and think that I didn't want to be involved" (#25, RA, three children- twins age 5 years and a baby age 1 month).

Two women described the difficult balancing act and feeling of "double trouble" when combining motherhood with a chronic disease as this:

> "It's challenging to be tired from having a toddler and being sick at the same time. I'm fully depended on my husband, who has been absolutely fantastic, not to break down" (#130, SpA, one child age 10 months).

> "Lack of sleep is probably normal when having small children, but when the bechterew disease also wakes you up at night, it can be challenging" (#120, SpA, one child age 2 years).

The difficult balancing act stands out as an overarching main theme that is further divided into five sub-main themes as illustrated in Table 2, and described in further detail below.

3.1.1 "Just everyday things"

Many women described how their disease, with symptoms such as pain, stiffness and fatigue, made everyday chores, as well as playtime and participating in activities with their children challenging. Having some physical limitations and difficulties with practical task was something that many of the women experienced to varying degrees since they developed IA. However, having challenges that affected their abilities to take care of their babies were described as a difficult and painful experience.

> "To sit down/bend down to the child, both during play and when dressing the child. Carrying/lifting the child, fastening in the car seat. Sitting down on the floor to play with the child. It is emotionally difficult when the child (and myself) have an expectation to do something, which is not possible due to physical limitations and pain, but which really is just everyday tasks such as dressing, playing, bending down to the child and so on. Of course, in most situation you will find alternative ways to do things, which might be a bit untraditional, but that works. But it's difficult at times to be a "different" mum, than "every other" mum. And baby-food, bottles, baby clothes should often have been more universally designed. I learned to avoid certain things because I had extra trouble with opening/buttoning etc." (#61, JIA, one child age 2 years).

Some felt that the challenges in relation to handling the baby grew as the children grew bigger:

TABLE 2 Qualitative results- main and subthemes.

Motherhood and rheumatic disease – a balancing act Challenges today, tomorrow and in the future				
1. Just everyday things	2. Feelings of inadequacy	3. Disease management	4. What about the future?	5. It's not that bad
- ADL[a] with small children - Playtime and activities	- Emotional challenges - Prioritizing self-care - Relations (family and work)	- Treatment and follow-up postpartum - Medications - Breastfeeding - Information needs	- Disease progression - Inheritance - Economy and work - Family planning	- Good medical treatment - Normal to be tired as a mother - Active lifestyle

[a]"Activities of daily living", here including feeding, changing and dressing, bathing/washing, carrying and handling the baby.

> "Now that the child is bigger everything has gotten more difficult: holding her, putting her to bed, bathing her…yes, basically everything. Lack power and strength and get a lot of pain after various tasks with her" (#151, SpA, one child age 8 months).

Activities and playtime also change, as the children grow older. For mothers who are struggling with pain and fatigue it can be difficult to keep up with the high level of energy and physical demands, as this woman explained:

> "Being tired, not having the energy to play, going for a walks, running after a bike and so on. This means there is less of these activities than what is normal. The child must be taken care of by others/their dad on days when everything is painful and tiring. It hurts not being able to take care of your own child all of the time" (#12, RA, one child age 4 years).

3.1.2 Feelings of inadequacy

Many women conveyed a strong feeling of inadequacy. This feeling was related to various aspects of their life as a mother with IA.

3.1.2.1 Emotional challenges

Not being able to be the mother they had pictured, and having trouble controlling their emotions due to pain and fatigue triggered many women to feel inadequate in their new role.

One mother expressed it like this:

> "It's a bit mentally challenging to realize you have limitations due to your illness that affect/will affect being a fully present mother. Feels like I'm failing somewhat in a role that I have chosen myself" (#130, SpA, one child age 10 months).

Another like this:

> "You feel like you are never good enough, having to say no to things that the children wants to do because you're simply in too much pain, and are always tired and exhausted. Spend a lot of energy pulling yourself together, so that the children don't see how much you're struggling with pain (…) You constantly have to pull yourself together on the worst days, so that you don't get angry with your kids and yell at them cause you are in pain. I often feel guilty because I feel I'm not patient enough and can get annoyed over little things" (#147, SpA, three children age 2, 5 and 8 years).

3.1.2.2 Relations – family and work

For some women the challenges and feelings of not being able to contribute and participate affected their relationship with their partner, and resulted in feelings of guilt and inadequacy.

These two women expressed it like this:

> "Me and my partner can get a shorter fuse between us. He has to do more. I don't have the capacity I used to. He gets up every morning. Aching makes it difficult to fall asleep at times. Sometimes it can be hard on our partnership" (#131, RA, two children age 1 and 3 years).

> "I often feel guilty that dad has to contribute more, especially in the mornings. And generally there's a bit too much responsibility on dad" (#29, RA, one child age 2 years).

Being able to work full-time was described as important for many of the women. However, several expressed combining full-time work with family-life and a chronic disease as difficult. One women wrote that she often prioritized work to look good for her employer even though this made the afternoons with her family very hard. Another felt constantly tired/exhausted and experienced it as difficult to be present when being with her family and children because she worked fulltime. Being able to work fulltime was also depended on the type of job, possibilities for making adjustments and having some flexibility:

> "If it wasn't for the fact that I have a very independent and flexible job (university-sector), I don't think I would have been able to be both a mum and an employee. I hope this survey can contribute to increased political focus on us with rheumatic disease with "double responsibility". For me, I think that only the possibility for rehabilitation in warm climate and/or some form of relief/childcare sometimes would make it possible to get enough a) rest and b) physical activity. I strongly want to work, also after giving birth to nr.2, but sometimes I worry that this won't be possible. I often feel alone with my diagnosis in everyday life, and as a woman I think that one can experience very different

> expectations about being able to deal with both work and family-life compared to men, despite the fact that we are in 2019" (#32, SpA, one child age 2 years).

3.1.2.3 Self-care

Focusing on self-care, such as exercise and resting, were emphasised as important and as a way of keeping their disease under control. Many women experienced that it was difficult or impossible to prioritize self-care, which again had a negative impact on their health; as this mother described:

> "I also feel/notice that to prioritize physical activity/exercise on my own has been difficult/non-existent, which in turn has a negative impact on my physical health and disease activity (…) With small children I also experience that there's no time to relax and rest, and that sleep is limited. I notice that this also affects me and my disease negatively" (#74, PsA, two children age 3 years and 1 year).

3.1.3 Disease management

Pregnancy and the postpartum period led to some new dilemmas and problems regarding disease management and medication use. A few women felt that they did not get sufficient information from health professionals leading to unnecessary distress. Information about medication use during pregnancy and breastfeeding was described as inadequate and often conflicting. Some felt they had to do their own research, in addition to involving their partners:

> "Decisions regarding medications, not enough knowledge among many of the doctors (especially regarding breastfeeding). I've used "tryggmammamedisin.no" ("Norwegian webpage with knowledge based information regarding medication in pregnancy and breastfeeding") to check if it´s ok" (#160, RA, two children age 3 and 1 year).

> "I also had bad conscience for my child because I took some painkillers prescribed by a doctor (very little), that the child's father meant wasn't good for the foetus. I felt I was "in a squeeze" where I experienced that the partner should get more information from the doctors, not just passed on by me" (#70, SpA, one child age 2 years).

Several expressed that they received insufficient information, making it challenging to manage their IA. The women wanted clear and understandable information, not only that it was important to stop certain medications during pregnancy, but also about alternatives.

> "I had been asked many times if I was planning to get pregnant, but that was just concerning that I had to stop my medications in time, never to tell me that there were alternatives if I did get pregnant. When I then got pregnant and came on a routine follow up appointment to the rheumatologist, I was met by a doctor who questioned why I hadn't let them know earlier. I said it as it was, that I didn't know that there was any reason to let them know – cause I didn't know that there was anything that they could do to help. Now I'm pregnant again and I feel I'm much more informed this time" (#124,RA, two children age 10 and 2 years).

Others described struggles with taking care of their babies after giving birth due to disease flares and inadequate follow up or treatment plans.

> "I would have appreciated a better plan regarding medication and treatment after birth and before stopping breastfeeding. I wasn't physically able to take care of the baby on my own until several months after birth, I wasn't prepared for this" (#77, PsA, one child age 1 year).

3.1.4 What about the future?

Naturally, having children and a family brought some new thoughts about the future. Several were concerned about the disease progress, and how their IA could affect their children and family in the future. The unpredictability of the disease worried them, making them questioning whether they were able to combine motherhood with a fulltime-job. If they could not work full-time, they were anxious about the economic consequences:

> "Unpredictability with regards to daily fluctuations in disease burden. Worries about worsening of the disease and that I will not be able to follow up the children" (#193, JIA, 2 children age 5 and 1 year).

> «Worry a lot about how the economic situation will be if I can't work fulltime in the future2 (#1, SpA, one child age 1 year).

> «I am dreading going back to work. I want to function as a mother and a girlfriend, and I think my work is going to take a lot of my energy" (#116,RA, one child age 1 year)

Several women also feared that their children would inherit their disease. Some described feelings of guilt if this would happen even though it was beyond their control. Whether to have more children or not is a life changing decision. Many of the women struggled to make such a decision because their prior pregnancy or post-partum periods were challenging, and they were unsure if they would go through it again:

> «I'm scared that the children may have inherited the disease, don't want them to be in pain just because I brought them into the world" (#209, PsA, two children age 2 years and 3 months).

> "I want my child to have siblings, but having to go through a heavy pregnancy and the pain afterwards makes me doubt" (#116, RA, one child age 1 year).

3.1.5 It's not so bad

Even though many women described difficulties in their role as a mother with IA, some described a more nuanced and positive picture of the situation. Better treatment, family-support and a perspective that normalised feeling tired a natural part of being a parent, independent of having a chronic disease, were mentioned.

Several women expressed that having a good medical treatment plan had significantly improved their lives with IA:

> "I'm much better after starting biologics. I live more or less like normal" (#154, SpA, one child age 5 months).

> "More challenges after the birth of my two first children (born 2011 and 2013), and in the first years, than after my last child (born 2018). Started biologics after giving birth in 2018, and this has given me a whole new life"(#10, RA, three children age 8, 6 and 2 years).

While some women were a bit concerned about whether their partner took too much responsibility, leading to stress on the relationship, others expressed that the support from their partner made the situation easier. Being a mother could be difficult and demanding at times regardless of having a chronic disease. Some women reflected on this, and that it could be difficult to know whether the challenges were due to their disease or to motherhood in general:

> "I've been lucky when it comes to my arthritis, so I don't think it affects me that much + I'm lucky to have a husband who takes care of the children when I'm tired (which doesn't happen very often)" (#189, JIA, two children age 2 and 6 years).

> "I think it's difficult to tell what is due to the disease and what is "just being a mother with small kids". Most people in this phase are tired" (#103, RA, three children age 12, 10 and 2 years).

Several also mention, despite the challenges, that having children led to a more active lifestyle, which had a positive impact on the disease symptoms:

> "At the same time I've experienced that having an active lifestyle, which you do when your home with small kids, is overall a good thing for the joints. I notice little from the disease during the day when I'm carrying, going for walks, playing and running. Its first when I sit down at night and when I wake up in the morning that I notice that I have a rheumatic disease" (#88, RA, 2 children age 3 and 1 year).

4 Discussion

The aim of this study was to gain insight into the challenges that mothers with IA encounter in their daily life. Many describe difficulties, both physically, mentally and socially that have a large impact on their everyday life. They describe life as a mother with a chronic rheumatic disease as a balancing act, trying to live up to the needs and expectations of their children, family and workplace, at the same time as they try to take care of their own needs in order to function in everyday life.

Experiences and expectations surrounding motherhood are strongly influenced by the culture and society one lives in. Norway is a welfare state, with universal healthcare and a developed system for parents with paid parental leave for up to a year, a free infant healthcare-programme and highly subsidised child-care (23). Studies on Norwegian cohorts of women with psoriatic arthritis, juvenile idiopathic arthritis and spondyloarthritis found altogether low and stable disease activity during pregnancy and the first year after birth (24–26). These are all important factors that potentially influence how Norwegian women with IA experience motherhood. Still, our findings are in line with previous qualitative studies on similar patient groups from other countries, reporting many of the same challenges (10, 12–16). Also Barlow et.al study from 1999 (15), going 25 years back, describe many of the same challenges as our cohort when it comes to parenting with small children. Troubles with everyday tasks, and feelings of guilt for missing out on activities, as well as frustration and inadequacy were also described in this study. Considering the vast improvement in medical treatment for patients with IA in the last two decades, also during pregnancy and breastfeeding (4, 19, 20, 27), one could assume that the described experience of motherhood also should improve. It is however clear from the literature, that despite recent improvements in medical treatment, many IA patients, including those with low disease activity/in clinical remission, have residual symptoms and significant unmet needs (28, 29). Studies have also shown that women with IA overall have a higher disease burden and more unmet needs compared to men (30).

The biopsychosocial model is helpful for clinicians to understand the complexity of how women with IA experience motherhood, and why improvement in medical treatment does not solve all of their challenges. Figure 1 illustrates various elements that has an impact on how women experience motherhood. The relations between the underlying factors are dynamic and intertwined. Many of these factors are relevant for how people with IA experience life with a chronic disease in all life stages, and pregnancy and motherhood can affect and intensify many of these elements contributing to the overall experience. When it comes to the psychological impact of having IA, studies have shown that people with IA are generally more at risk of both depression and anxiety disorders (31) and mothers with IA are more at risk of developing postpartum depression compared to mothers without IA (32, 33). In addition, poor mental health is linked to worse outcomes in IA (34, 35). We do not know if any of the women in this study had a comorbidity of anxiety or depression, but it is plausible that some did, and that this potentially affected their experience of motherhood.

Many women in our study expressed difficulties with prioritizing self-care and exercise, which had a detrimental effect on their function and disease activity, also contributing to the experience of inadequacy. The majority of the women in our study were also working, making prioritizing self-care even more challenging. The

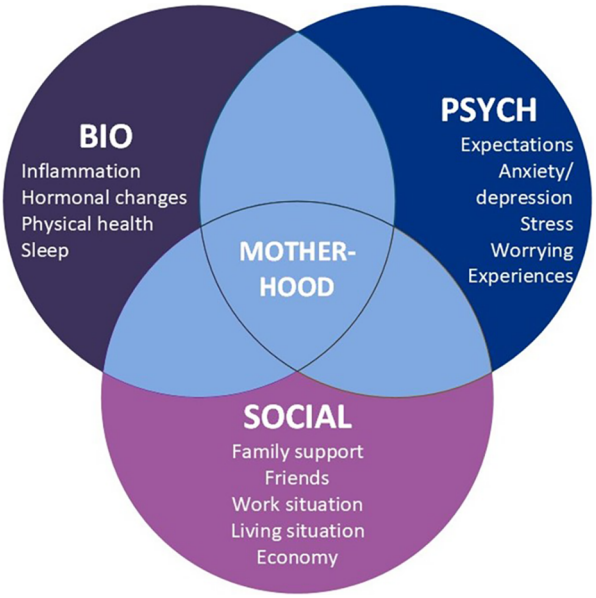

FIGURE 1
Illustration of elements affecting how women with IA experience motherhood, in a biopsychosocial framework.

cultural expectations of motherhood in the western society, and how this affects women with various health challenges is thoroughly discussed in several studies (14, 36, 37). Attending to and prioritizing own needs, e.g., with exercise and resting, rather than always attending to their children and others needs first, means that the women might not live up to their own and their perceived expectations of others in the role as a mother.

A study by Bar and colleagues (38) gave some interesting insight from men with IA, and their experience of fatherhood. Despite arthritis interfering with specific tasks for these men in the same way that mothers in our study describe, it did not affect the way they perceived themselves as fathers. Strong social support, ability and possibility to prioritize themselves in regards to things such as exercise and rest, and taking ownership of their disease by changing priorities, pacing activities and normalizing their disease were all factors that contributed to a predominantly positive experience of fatherhood. Going back to the biopsychosocial model, these men expressed many positive experiences in the psychosocial domains, illustrating how these can be protective and positive factors in the overall experience of being a parent with IA. It is interesting that several women in our study felt guilty when the dad had to step in and at times do more, such as get up in the morning. No men in Bar et al. study mentioned feelings of guilt and they were not hesitant about seeking and accepting help and support, possibly a result of cultural expectations and differences in parenteral role of mothers vs. fathers (39).

Challenges with disease management and follow-up in relation to pregnancy and the post-partum period, as well as insufficient/contradictory information from various health professionals was brought up as problematic by many women in our study. This can lead to uncertainty and increased stress and worrying, non-compliance, increased disease activity and feelings of inadequacy, illustrating how everything is connected. The findings in this study adds to an already extensive number of studies highlighting problems with unmet information and support needed for this patient group (17, 40–42).

Empowering these women, and learning them good self-management strategies in order to deal with the practical, physical and psychological challenges they encounter in their role as a mother with a chronic disease is vital. Pregnancy and the post-partum period represents a massive life-changing event. EULARs recommendations on patient education (PE) for patients with IA (43) states that PE should be provided as an integral part of their care to increase patient involvement in disease management. They also highlight that the need for education and support might be more prominent when the disease interferes with daily activities, life-events and family roles, and that PE should include discussion on emotional issues and support. Increased focus on PE and self-management interventions in relation to pregnancy and the postpartum period is thus something that should be prioritized (3, 43, 44).

The findings in this study highlights the importance of providing high quality multidisciplinary care with a holistic and individualized approach for this group of patients, where the health care professionals have insights into the common challenges these women encounter. The team of health care professionals should provide advice and guidance on practical aspects of childcare, physical activity, exercise, patient rights, adjustments in work life, patient information, self-management and optimal medical treatment (17). Also encouraging the women to get in touch with peers through i.e., patient organisations, can be of great value (44).

4.1 Strengths and limitations

One of the main strengths in this study is that 186 of the 233 women responded to the open-ended question providing us with a rich material of written descriptions of experienced challenges among mothers with IA. On the other hand, a possible limitation with the written responses is that we were not able to ask the respondents to elaborate, as qualitative interviews could have, limiting the depth of the data (45). The open-ended question encouraged the respondents to write about their challenges related to being a mother with IA, and positive experiences might not be captured.

Even though the experiences described in this study do not apply to all women with IA, they provide great insights that are beneficial for clinical practice in further development of follow-up care.

This study only included Norwegian mothers. This might limit the reproduction of these results in other locations, especially less developed countries.

4.2 Recommendations for future research

This study gives valuable insights into the experienced challenges among mothers with IA. Hence, further studies should

focus on the positive experiences of motherhood; on beneficial strategies to improve different challenging situations, and how health care personnel can best support women in planning their pregnancy, during pregnancy, and in the post-partum period. The experiences of becoming a father when living with IA is also less studied, and what kind of support they need in this phase of life.

Comparing the experiences and challenges of mothers with IA to women with other chronic diseases, or to healthy mothers could also give important insight into what challenges are unique to those living with IA, and what challenges are common for mothers regardless of diagnosis.

5 Conclusion

The main finding in this study is that the women with IA experience several challenges related to motherhood. The challenges are multifactorial and complex, including physical, mental and social issues that have a large impact on their everyday life. Focusing solely on improving medical treatment will not solve the challenges these women face. A multidisciplinary approach and focus on patient education and self-management strategies is important to help these mothers thrive in their role as a mother with chronic disease.

Data availability statement

The datasets presented in this article are not readily available because The data cannot be shared publicly due to the requirements of the involved register holders and the general data protection regulation, to protect the privacy of individuals. Requests to access the datasets should be directed to ingrid.rekaa.nilssen@stolav.no.

Ethics statement

The studies involving humans were approved by Regional Committee for Medical and Health Research Ethics South/East Norway. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

IN: Conceptualization, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing, Formal Analysis, Investigation, Visualization. HK: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. BJ: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. KG: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Insights into pregnancy risks associated with active juvenile idiopathic arthritis

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KEYWORDS

active juvenile idiopathic arthritis, preeclampsia, fetal growth, disease activity score with CRP, medical birth registry of Norway

Dear Editor

The study by Götestam Skorpen et al. (1) represents a significant contribution to our understanding of how juvenile idiopathic arthritis (JIA) affects pregnancy outcomes. By leveraging a robust dataset from Norwegian registries, the authors effectively address a critical gap in the literature regarding the implications of active JIA during pregnancy. However, while the strengths of the study are commendable, there are limitations that warrant further discussion.

This study demonstrates that women with active JIA face a significantly higher incidence of preterm birth, recorded at 17.6%, compared to a rate of 4.9% among control participants. This finding aligns with previous research conducted by Remaeus et al. (2) and Smith et al. (3). Notably, there were no reported cases of preeclampsia in either the active or inactive JIA cohorts, which corresponds with studies by Förger et al. (4) and García-Fernández et al. (5), despite earlier literature suggesting a potential elevated risk. Additionally, the study identified heightened rates of gestational hypertension in both active (7.2%) and inactive JIA groups compared to controls (1.7%), consistent with findings from Drechsel et al. (6) and Mohamed et al. (7). There were no significant differences in abnormal fetal growth between the JIA and control groups, supporting earlier studies by Remaeus et al. (2) and Chen et al. (8). The current research highlights the significant impact of disease activity in JIA, indicating that active JIA is associated with an increased risk of certain adverse pregnancy outcomes. Conversely, inactive JIA does not exhibit the same level of risk. This conclusion is corroborated by prior studies that suggest improvements in the management and treatment of JIA during pregnancy may have favorably affected these outcomes.

One of the primary strengths of the study is its large sample size, which enhances the reliability and generalizability of the findings within the Norwegian context. This allows for more confident conclusions to be drawn about the differences in pregnancy outcomes between women with active JIA and healthy controls, as well as those with inactive disease. The clear objectives focused on specific adverse outcomes—such as preterm birth and gestational hypertension—provide a structured framework for the analysis, making it easier for healthcare providers to understand the risks involved.

The inclusion of disease activity assessments using the Disease Activity Score with CRP (DAS28-CRP-3) during the second and third trimesters is particularly noteworthy. This suggests that the researchers are mindful of the variability of disease activity throughout

pregnancy and its potential effects on outcomes. However, the limitation regarding the lack of early pregnancy disease activity assessment could be significant. Many factors that contribute to pregnancy complications may be influenced by the disease status in the first trimester, which can set the stage for how the pregnancy will progress. This aspect raises questions about the timing of interventions and monitoring for women with JIA to optimize outcomes.

Furthermore, the absence of an analysis of JIA subtypes is another notable limitation. JIA encompasses several subtypes, each with distinct characteristics and disease courses. Understanding how these differences influence pregnancy outcomes could guide personalized management plans for expecting mothers with JIA. Without this analysis, the study may overlook critical nuances that could alter interpretation and recommendations for different patient groups.

The authors' study on JIA in adults highlights significant limitations, particularly in assessing disease activity. Concerns arise over the validity of the DAS28-CRP-3 for adult JIA populations, especially regarding potential misclassification of disease activity and its implications for treatment decisions. The absence of disease activity evaluations during early pregnancy is also critical, as hormonal changes can greatly affect disease behavior. Furthermore, the study fails to distinguish between JIA subtypes, such as polyarticular and oligoarticular JIA, which have unique clinical characteristics and treatment responses. Addressing these issues in future research is vital for improving understanding and care for women with JIA during pregnancy.

The researchers highlight increased risks of preterm birth and gestational hypertension, while their findings on preeclampsia and fetal growth are intriguing. It is surprising that women with active JIA do not exhibit a higher risk for preeclampsia, given the known links between chronic inflammation and pregnancy-related hypertensive disorders. This finding warrants further investigation, as it may point to protective factors in the JIA population or reveal the complex relationship between inflammation and pregnancy physiology. However, a significant limitation of the study is its reliance on the Medical Birth Registry of Norway (MBRN) for identifying JIA cases through ICD-10 codes, which can lead to inaccuracies. Misclassifications may arise from coding errors, diagnostic criteria variations, or differences in clinical practices, potentially skewing the prevalence of JIA and its maternal and neonatal outcomes. The ICD-10 system may overlook nuanced aspects of JIA, particularly in ambiguous cases or those overlapping with other rheumatic diseases, potentially excluding true JIA patients and distorting results. The timing of diagnosis is also crucial; if JIA is identified post-pregnancy registration, vital data may be missing from MBRN, creating gaps in understanding its effects on pregnancy outcomes. The authors' failure to address this limitation could lead to an overestimation of the study's implications regarding JIA and pregnancy, suggesting that a thorough discussion of ICD-10 coding inaccuracies would bolster the study's credibility and provide insights for future research on rheumatic diseases in pregnancy contexts.

Lastly, while the study is well-designed within Norway's healthcare framework, its generalizability to other populations is uncertain. Differences in healthcare systems, access to care, and cultural attitudes toward managing chronic diseases during pregnancy may affect outcomes in varying contexts. Therefore, caution is recommended when extrapolating these findings to women with JIA in other countries.

In conclusion, the study by Götestam Skorpen et al. adds to the growing body of literature regarding JIA and its implications for pregnancy outcomes. It underscores the vital role of active disease management during pregnancy for improving maternal and fetal health. However, the limitations discussed reveal areas for further research that could enhance our understanding and inform clinical practice. Additional studies that focus on early disease activity assessment, subtype differences, and international comparisons will be essential for developing comprehensive care strategies for pregnant women with JIA.

Author contributions

MY: Conceptualization, Writing – review & editing. RB: Conceptualization, Writing – original draft. SES: Methodology, Writing – original draft, Writing – review & editing. HN: Data curation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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High fetal risk in pregnancies of myositis patients—a Hungarian cohort study

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Background: Several systemic autoimmune rheumatic diseases may affect both fetal and maternal outcomes during pregnancy. However, little information is available regarding pregnancy outcomes in women with idiopathic inflammatory myopathy. Previously published articles stated that the activity of maternal disease may worsen pregnancy outcomes. A former multicenter study suggested that anti-Jo1 antibody positivity and joint involvement could distinguish a more vulnerable group regarding pregnancy complications. Our aim was to identify prognostic factors among clinical symptoms at disease onset and auto-antibody profiles for identifying a high-risk group for poor pregnancy outcome.

Methods: The clinical data of the myositis cohort of the Division of Clinical Immunology, University of Debrecen, Hungary, were reviewed retrospectively. IIM diagnoses were made by Bohan and Peter's criteria or European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) criteria. Disease activity was evaluated based on physician opinion. Gynecological definitions were used to evaluate fetal outcomes.

Results: Reviewing clinical data of overall 763 patients (542 women and 221 men) revealed that 5.2% of female patients had pregnancies in the same time or after myositis onset. Among these, 71.4% of the mothers suffered from polymyositis (PM) and 28.6% suffered from dermatomyositis (DM). Their mean age at the time of myositis diagnosis was 25.28 years, and the average interval between myositis diagnosis and first pregnancy was 55.4 months. Maternal complications included preeclampsia in one case and pregnancy-induced myositis in 25% of cases. All cases of pregnancy-induced myositis improved after immunosuppressive treatment. Twenty-eight patients reported 60 pregnancies overall, with multiple pregnancies occurring in 57% of cases. Early or late fetal loss was detected in 41.7% of the pregnancies, and stillbirth occurred in 18.3% of deliveries. Although late fetal loss was observed mainly due to placental insufficiency in patients with anti-Jo1 positivity and complications seemed more frequent in PM cases, logistic regression analysis only confirmed that multiple pregnancies could be an independent risk factor for fetal ($p = 0.0112$) and interstitial lung disease of maternal complications ($p = 0.02$).

Conclusion: Internal organ involvement and the number of pregnancies could influence pregnancy outcomes in myositis patients. Patients' family planning should be well organized and counseled by myositis experts. Prospective, multicenter collaborations are needed to precisely identify high-risk groups and state managing guidelines.

KEYWORDS

polymyositis, dermatomyositis, pregnancy, outcome, miscarriages, internal organ involvement

Introduction

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of systemic autoimmune rheumatic diseases (SARDs) characterized by progressive muscle weakness and specific skin symptoms. Internal organs, including the skin, joints, lungs, heart, and gastrointestinal tract, can also be affected in both skin-dominant [dermatomyositis (DM)] and muscle-dominant forms [polymyositis (PM)] (1).

Like other SARDs, idiopathic inflammatory myopathies may affect both fetal and maternal outcomes during pregnancy. Probably due to the rarity of the disease or its later onset, there is only one short consensus guideline for planning and managing pregnancy in these patients (2). Correlations between clinical and pathological alterations have been barely studied. Based on previous studies, only 12%–29% of IIM cases are recognized during the reproductive years (3–6). A couple of retrospective cohort studies revealed that the activity of maternal disease could worsen pregnancy outcomes (3–10). Complete remission refers to a better fetal outcome (1), while high disease activity increases abortion rates above 50% (7) and increases the risk of stillbirth or neonatal death (5). Our former multicenter study suggested that anti-Jo1 antibody positivity and joint involvement could distinguish a more vulnerable group considering fetal pregnancy complications (8). Except pregnancy induced myositis cases maternal outcome is generally favorable (9). Based on several case series and reports, "pregnancy-induced" myositis could be a leading risk factor considering maternal outcomes (3–11). A population-based study reported an increased risk of hypertensive disorders of pregnancy in patients with DM/PM compared with the general population (OR = 2.18, 95% CI: 1.37–3.46) (10). No data are available concerning medication risks during and after pregnancy or the effect of myositis on breastfeeding.

Our aims were to evaluate the frequency of maternal and fetal pregnancy complications in myositis, find prognostic factors of maternal and fetal complications among clinical symptoms and auto-antibody profiles, and identify high-risk groups for unfavorable pregnancy outcomes.

Materials and methods

A retrospective data analysis of the myositis cohort at the University of Debrecen was used to assess the frequency and outcome of pregnancies after IIM onset. Clinical data from 763 patients (542 women and 221 men) diagnosed between 2000 and 2022 were reviewed.

IIM diagnoses were made using Bohan and Peter's criteria or EULAR/ACR diagnostic criteria. Myositis-specific and associated auto-antibodies were identified by ELISA and immunoblot techniques; anti-phospholipid (APL) antibodies, including anti-b2glycoprotein IgG and IgM, anti-cardiolipine IgG and IgM, and thyroid-specific antibodies [anti-thyroperoxidase (TPO)], were detected using the ELISA technique. Detection of lupus anticoagulant (LAC) was made by dilute Russell's viper venom time (dRVVT) test. Disease activity was evaluated and recorded in medical files based on clinical symptoms, muscle enzyme levels, and physician opinion before 2011 and using International Myositis Assessment and Clinical Studies Group (IMACS) core set measures thereafter. As this is a retrospective cohort study when disease activity was evaluated with different methods for statistical analysis, patients were categorized into active and inactive groups. Pregnancy data were self-reported by the mother and supplemented with medical records. Pregnancy-induced myositis was defined as IIM symptoms that began during pregnancy or within 6 months following delivery or termination.

Data on general maternal complications, such as gestational diabetes, hypertension, preeclampsia, eclampsia, and excessive bleeding, were recorded. Also, disease-specific complications, such as weak contractions, pregnancy-induced myositis, relapses, or worsening of clinical symptoms, were collected.

Gynecological definitions were used to evaluate fetal outcomes. Normal labor was defined as the delivery of a healthy newborn weighing >2,500 g after 37 weeks of pregnancy. Stillbirth was defined as the end of a pregnancy between gestational weeks 28 and 37. Abortion or miscarriage was defined as a pregnancy ending before 28 weeks, without specification as spontaneous or induced. Early pregnancy losses occurred in the first trimester, and late losses occurred in the second trimester. We considered pregnancy losses observed in the third trimester as fetal deaths.

After descriptive statistics, Fisher's exact test was used to prove univariate associations and logistic regression analysis was conducted to identify independent risk factors for fetal and maternal complications. Myositis subset, maternal age, organ involvement, auto-antibodies, number of pregnancies, and disease activity were included in the analysis.

Results

General myositis characteristics

Data collection revealed that 5.2% ($n = 28$) of the 542 female patients had pregnancies either concurrently with or after myositis onset. Among these, 71.4% ($n = 20$) suffered from polymyositis and 28.6% ($n = 8$) suffered from dermatomyositis. Their mean age at the time of IIM diagnosis was 25.4 years. A total of 75% ($n = 21$) of patients had a longer history, with an average disease duration of 55.4 months, while 25% ($n = 7$) of women suffered from pregnancy-induced myositis. Half of the DM patients had a juvenile-onset disease. The most common clinical symptoms were muscle weakness (96%; $n = 27$), arthralgia (64%; $n = 18$), and Raynaud's phenomenon (54%; $n = 15$). Skin rashes, interstitial lung disease, and dysphagia are classified as rare manifestations. Table 1 presents the basic demographic data of the cohort. There were no significant differences in clinical and serological characteristics. Multiple pregnancies were more frequent in the PM subset than in DM (70% vs. 25%; $p = 0.04$). No therapy refractory cases have been reported. Based on the opinion of the treating physician, mild or moderate disease

TABLE 1 Basic clinical and serological data of our cohort.

	Full cohort	PM	DM	Difference between PM/DM subsets
Case number	28	71.4% ($n = 20$)	28.6% ($n = 8$)	na
Mean age (years)	25.4	25.2	25.5	ns
IIM disease duration before pregnancy (months)	55.4	41.5	90	ns
Pregnancy-induced cases	25% ($n = 7$)	30% ($n = 6$)	12.5% ($n = 1$)	ns
Clinical symptoms				
Muscle weakness	96% ($n = 27$)	100% ($n = 20$)	87.5% ($n = 7$)	ns
Arthralgia	64% ($n = 18$)	70% ($n = 14$)	50% ($n = 4$)	ns
Raynaud phenomenon	54% ($n = 15$)	60% ($n = 12$)	37.5% ($n = 3$)	ns
Skin rashes	43% ($n = 12$)	20% ($n = 4$)	100% ($n = 8$)	$p = 0.002$
Interstitial lung disease	25% ($n = 7$)	35% ($n = 7$)	0%	ns
Dysphagia	14% ($n = 4$)	10% ($n = 2$)	25% ($n = 2$)	ns
Fever	7% ($n = 2$)	10% ($n = 2$)	0%	ns
Myocarditis	4% ($n = 1$)	5% ($n = 1$)	0%	ns
Antibody profile				
ANA	82% ($n = 23$)	85% ($n = 17$)	75% ($n = 6$)	ns
Myositis-specific antibodies	39% ($n = 11$)	45% ($n = 9$)	25% ($n = 2$)	ns
Anti-Jo1	73% ($n = 8$)	40% ($n = 8$)	0%	ns
Anti-SRP	9% ($n = 1$)	5% ($n = 1$)	0%	ns
Anti-SAE	9% ($n = 1$)	0%	12.5% ($n = 1$)	ns
Anti-Mi2	9% ($n = 1$)	0%	12.5% ($n = 1$)	ns
Myositis-associated antibodies				
Anti-SSA	39% ($n = 11$)	50% ($n = 10$)	12.5% ($n = 1$)	ns
APL	43% ($n = 12$)	40% ($n = 8$)	50% ($n = 4$)	ns
LAC	0%	0%	0%	ns
Other (anti-TPO)	21% ($n = 6$)	30% ($n = 6$)	0%	ns
Pregnancy outcome				
No fetal or maternal complications	46% ($n = 13$)	35% ($n = 7$)	75% ($n = 6$)	ns
Maternal and fetal complications	14% ($n = 4$)	15% ($n = 3$)	12.5% ($n = 1$)	ns
Maternal complications (in one or more pregnancies)	25% ($n = 7$)	30% ($n = 6$)	12.5% ($n = 1$)	ns
Fetal complications (in one or more pregnancies)	43% ($n = 12$)	50% ($n = 10$)	25% ($n = 2$)	ns
Multiple pregnancies	57% ($n = 16$)	70% ($n = 14$)	25% ($n = 2$)	$p = 0.0441$
Documented disease activity before or during pregnancy	46% ($n = 13$)	55% ($n = 11$)	25% ($n = 2$)	ns

na, not applicable; ns, not significant.
p denotes statistical significance.

activity was identified in 46% ($n = 13$) of cases before or after conception. Muscle enzyme levels varied from normal to slightly elevated, with no significant correlation to pregnancy outcomes. Check-ups were organized at various intervals, unfortunately lacking consistency. No mothers were on teratogenic medication before pregnancy or at the time of conception. Corticosteroids alone or in combination with azathioprine, cyclosporine A, and/or intravenous immunoglobulin (IVIg) were used. During and after pregnancy, mothers were either treatment-free (11%; $n = 3$), treated with corticosteroid only (64%; $n = 18$), or treated with corticosteroid and azathioprine combination (25%; $n = 7$). One mother had been on methotrexate before conception, but it was discontinued when they were planning the pregnancy. One mother was on cyclophosphamide therapy due to interstitial lung disease (ILD) at the time of conception, and this pregnancy ended in miscarriage. Due to variations in medications, we have excluded them from statistical analysis. Low-molecular-weight heparin (LMWH) and low-dose aspirin (100 mg) were also used in APL-positive cases after pregnancy pathology, as former APL guidelines suggested.

Immunofluorescent staining of blood samples showed that 82% ($n = 23$) of women with pregnancy complications were positive for antinuclear antibodies (ANAs). In total, 11% ($n = 3$) of women had no detectable auto-antibodies in their serum before pregnancy. A total of 36% ($n = 10$) of them had a single (mostly anti-phospholipid) antibody, while 54% ($n = 15$) showed multiple antibody positivity. Lupus anticoagulant analysis was performed in only 75% of cases ($n = 21$), but all results were negative. Myositis blot analysis revealed myositis-specific (39%; $n = 11$) and myositis-associated (50%; $n = 14$) antibodies. Detected IIM-specific antibodies were anti-Jo1 (73%; $n = 8$), anti-SAE, anti-Mi2, and anti-SRP in individual cases. Among myositis-associated antibodies, anti-SSA was detected as frequently as myositis specific antibodies (MSA) (39%; $n = 11$).

Maternal outcomes

In general, maternal outcomes in IIM were favorable. Preeclampsia was reported in only one case. Pregnancy-induced

IIM was reported in 25% of all cases, with 42% ($n = 3$) in the first trimester, 29% ($n = 2$) in the third trimester of pregnancy, and 29% ($n = 2$) after delivery or termination. No variable showed a significant association with maternal complications in univariate testing. Interstitial lung disease was identified as an independent risk factor for maternal complications (OR: 12; 95% CI: 1.48–97.18; $p = 0.02$) by logistic regression analysis. All pregnancy-induced cases improved with individualized immunosuppressive treatment. The most frequently used drug was intravenous corticosteroids in these cases; high-dose IVIg was used in one severe case when the mother presented with new-onset anti-phospholipid syndrome accompanied by myositis, arthritis, fever, and interstitial lung disease.

Fetal outcomes

In the case of our 28 patients, 73 pregnancies were recorded, 60 of which were conceived after IIM onset. Patients did not report any pregnancy complications before myositis symptoms. Multiple pregnancies occurred in 57% ($n = 16$) of cases. In contrast to favorable maternal outcomes, depressing fetal results were found (Figure 1). Only 58% ($n = 35$) of pregnancies ended with delivery, with one-third of the delivered babies being born prematurely. Stillbirth was reported in 18.3% of all pregnancies and in 31.4% of labors. Early or late fetal loss was detected in 41.7% of the pregnancies ($n = 25$). In the first trimester, we only recorded miscarriages, along with one case of induced abortion due to high maternal disease activity. Unfortunately, no gynecological reports are available considering the potential causes of these pregnancy losses. All 12 patients who experienced miscarriages were auto-antibody-positive (anti-Jo1, anti-SRP, anti-TPO, and APL). Among patients with fetal pregnancy complications, 50% ($n = 7$) were APL-positive, but there were no significant differences considering fetal complications in APL-negative cases. LAC testing was performed in 75% of all patients, but all results were negative. Of the seven patients who were not tested for LAC, only one reported miscarriages. High disease activity before pregnancy was reported by the treating physician in only three cases.

Late pregnancy losses, which placed a more excessive physical and mental burden on the mothers, were reported in seven pregnancies across five women. They all were treated with proper immunosuppressive medication and had no or mild disease activity. In the cases where full gynecological descriptions were available (only four of these seven pregnancies), fetal death was associated with placental insufficiency due to early calcification or circulation issues. Late pregnancy loss was mostly observed in patients suffering from anti-synthetase syndrome ($n = 3$). Histopathological examination of the placenta is rare, even after fetal death. Placental insufficiency was associated with various histological findings. We also recognized a rare pathological manifestation, massive perivillous fibrinoid deposition (MPVN, Figure 2), in the placenta in the case of a woman suffering from anti-synthetase syndrome and anti-SSA antibody positivity who had experienced several pregnancy losses.

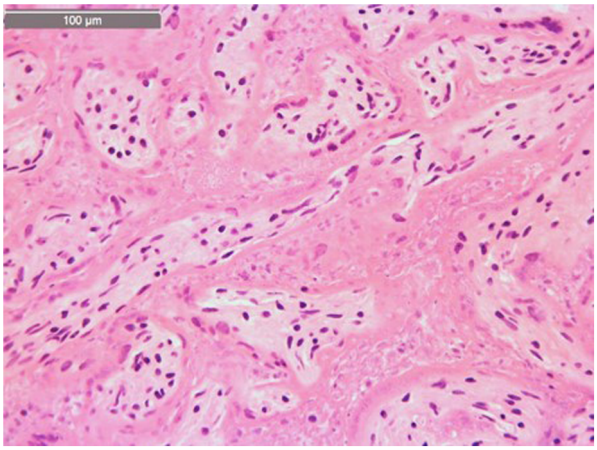

FIGURE 2
MPVN as a sub-phenomenon of placentitis by hematoxylin-eosin staining from the archive of our pathology institute.

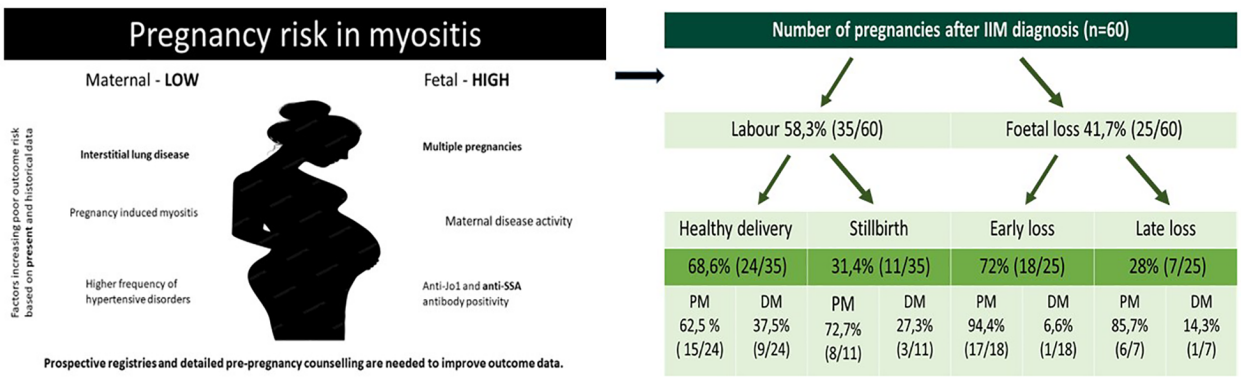

FIGURE 1
Main causes of maternal and fetal complications reported previously and in this study (bold); and different fetal complications during pregnancies of IIM patients in the Hungarian cohort.

In cases of pregnancy-induced myositis ($n = 7$), four stillbirths and two early miscarriages were reported. These mothers also experienced complications in subsequent pregnancies, regardless of disease activity.

Reviewing polymyositis patients' medical documentation fetal complication have been found twice frequent than healthy deliveries (31 complications vs. 15 healthy baby). This ratio was 9 healthy baby vs. 5 fetal complications in patients suffering from dermatomyositis. Although complications seemed more frequent in PM cases, results did not reach statistical significance. Univariate analysis showed that anti-SSA antibody positivity was significantly more frequent in patients with fetal complications (17.6% vs. 66.7%; p: 0.014). Logistic regression analysis confirmed that multiple pregnancies could be an independent risk factor for fetal complications (OR: 4.19; CI: 1.39–12.69; $p = 0.0112$). Based on our data, a poor outcome in a first pregnancy is associated with poor outcomes in subsequent pregnancies. The cause of repeated poor outcomes could not be revealed by our data.

Discussion

Detailed reports on pregnancy outcomes and complications in patients with idiopathic inflammatory myopathies are scarce. Based on our large cohort, we can assume that maternal outcomes in pregnancies of IIM patients appear favorable. Neither our cohort nor previously reported ones exhibited specific maternal complications (3–9, 11–17). As an exception, Kolstad et al. published a population-based study concluding that IIM patients have longer hospitalization during delivery and an increased risk of hypertensive disorders, including preeclampsia and eclampsia, but no increased risk for fetal complications (10). In other reports, similar to our cohort, disease relapse or onset during or shortly after pregnancy was considered a risk for maternal health.

On the contrary, IIM is considered a high-risk group regarding fetal complications. A limitation of this study is the retrospective design and the heterogeneity of medical documentation. Reviewing the literature in this research field, we can state that several fetal complications have been reported, and high fetal risks are not obviously associated with maternal disease activity. A recent review also stated that only 52.8% of pregnancies in IIM patients ended with the birth of a healthy child (4). Relatively poor pregnancy outcomes have been reported, including spontaneous/induced abortion in 27.6% of pregnancies, stillbirth/neonatal death in 7.5%, preterm birth in 12.6%, intrauterine growth retardation in 4.7%, and low birth weight in 7.4%. Among 159 pregnancies occurring after DM/PM onset, only 50 involved active disease. The difference in abortion rates (36% vs. 29.5%) between pregnancies with active disease and pregnancies with inactive disease did not reach statistical significance. However, the proportion of total fetal loss (48% vs. 35%, $P = 0.049$) was significantly higher in pregnancies with active maternal disease. Pregnancy-induced cases have also reported more fetal complications (31.4% vs. 67.2%) (5). Previous studies also mentioned high rates of abortion/miscarriage (43%–50%) and preterm births (6, 7, 11–16), mostly in women with active IIM. Even earlier studies revealed that pregnancies in patients with juvenile-onset IIM were associated with a high percentage of at-term births, while in women with adult-onset IIM before pregnancy, this percentage decreased to 50%. Among patients diagnosed with PM–DM during pregnancy, the percentage of live births was 38% (7, 14). A Swedish population-based study revealed about a threefold increased risk of preterm birth (particularly very preterm birth) and a sixfold increased risk of low birth weight in IIM patients compared with the non-IIM group (17). Because myositis core set measures (18), manual muscle test results, and creatine kinase (CK) levels are not reported in the above-mentioned articles, judgment about disease activity and its association with fetal outcomes is heterogeneous. Detailed antibody profiles of the patients are also missing.

Our results suggest that, in addition to disease activity, multiple pregnancies and disease characteristics also influence fetal outcomes, especially in relation to late pregnancy complications. The observed late fetal losses occurred only during pregnancies of antibody-positive mothers. Massive perivillous fibrin deposition is a rare sign of severe placentitis previously associated with anti-phospholipid syndrome and infections (19, 20). We have found some case reports describing this rare pathological finding in pregnancies of IIM patients. Hung et al. presented the case of a 20-year-old anti-Jo1-positive polymyositis patient who delivered a stillborn fetus and damaged placenta with MPVN (19). Krones et al. reported the case of a new-onset MDA-5-positive DM with skin, muscle, and lung involvement. During this women's pregnancy MPVN was also reported as histopathological background of fetal complication. She delivered a premature baby at 34 weeks via an emergency cesarean section due to decreased fetal movements and a non-reassuring fetal heart rate. The maternal disease was stabilized by corticosteroid, hydroxychloroquine, and JAK inhibitor treatment. However, no information about the infant's outcome was available (20). In contrast to these cases, our patient exhibited anti-Jo1 and anti-SSA antibody positivity, showed no signs of disease activity, and was on combined immunosuppressive therapy. Unfortunately, her pregnancy ended in fetal loss due to placentitis. Her other pregnancy ended in a preterm delivery, but fortunately with a healthy infant. The placental macroscopic and histological findings were the same. Another patient with anti-Jo1 and anti-SSA antibody positivity delivered a stillborn infant at 36 weeks due to placental hypoxia and circulation issues. In this case, an autopsy was not recommended by the obstetrician.

The role of anti-phospholipid antibodies and lupus anticoagulant in pregnancy complications among myositis patients remains unknown. A limitation of our study is the lack of data; however, all tested patients were negative for LAC, while 50% of patients with fetal pregnancy complications were APL-positive. Although IIMs are rarely associated with anti-phospholipid syndrome (21), we need prospective, well-organized studies to reach further conclusions.

Summarizing previous and current results, we can conclude that the risk of fetal complications in patients with myositis is high. Although the stillbirth rate in the general population

in Hungary is considered high (8%–9%) (22), this rate is even higher (31.4%) in our IIM cohort. There is an unmet need for prospective, detailed studies to identify the causal relationships between disease activity, organ involvement, auto-antibody profiles, and maternal outcomes. Close monitoring of pregnancies in IIM patients, even without disease activity and placenta autopsies after healthy or complicated pregnancies, could help explore the pathomechanism of placental insufficiency and decrease fetal complication rates. Prospective studies are needed to evaluate the connection between disease activity, serology profiles, myositis symptoms, and pregnancy outcomes. Family planning for these patients should be well organized and counseled by myositis experts, with multi-disciplinary collaborations and consensus guidelines to improve worrying fetal outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement

This study involving human participants was approved by the Regional and Institutional Ethics Committee, University of Debrecen (RKEB 6144-2022). The study was conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired primarily isolated as part of our previous study for which ethical approval was obtained. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

MN-V: Writing – original draft. DS: Data curation, Investigation, Writing – review & editing. KS: Data curation, Investigation, Writing – review & editing. SM: Visualization, Writing – review & editing. LB: Methodology, Writing – review & editing. TB: Data curation, Investigation, Methodology, Writing – review & editing. ZG: Supervision, Writing – review & editing.

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Conflict of interest

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Postnatal health of infants born to mothers with autoimmune diseases when treated with hydroxychloroquine

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Introduction: This retrospective cohort study aimed to observe the postnatal health of infants born to mothers with systemic autoimmune rheumatic diseases treated with hydroxychloroquine (HCQ) during pregnancy.
Methods: A total of 312 pregnancies of patients who suffered from different systemic autoimmune rheumatic diseases were considered. Pregnancy data were collected; a telephone follow-up questionnaire was successfully completed in 182 infants to detect the long-term pediatric outcome. The women who took hydroxychloroquine during pregnancy were defined as "HCQ group" and were compared to women who did not take hydroxychloroquine, "non-HCQ group".
Results: A higher prevalence of women with multiple maternal diseases was detected in the HCQ group, in comparison to that of non-HCQ group (p = 0.0015). Despite HCQ group consisting of more complicated maternal conditions, the obstetrical and neonatal outcomes were similar between the two groups. Regarding postnatal health, 40% of infants in HCQ group revealed no pathologies versus 25% of the children in non-HCQ group (p = 0.0368).
Discussion: The protective role of HCQ on infants should be further evaluated in prospective multicenter long-term studies.

KEYWORDS

hydroxychloroquine, postnatal health, pregnancy, autoimmunity, autoimmune diseases

Introduction

Hydroxychloroquine (HCQ) is an old antimalarial drug, that has reached wide employment for treating systemic autoimmune rheumatic diseases. HCQ blocks the interaction of memory B-cells but not naive B-cells. A major mechanism of HCQ is preventing complement system activation. Moreover, HCQ inhibits various endolysosomal functions, including autophagy, endosomal Toll-like receptor

Abbreviations
HCQ, hydroxychloroquine; aPL, antiphospholipid antibodies; SLE, systemic erythematosus lupus; APS, antiphospholipid syndrome; RA, rheumatoid arthritis; pSjS, primary Sjogren's syndrome; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease; AZA, azathioprine; VAPS, vascular antiphospholipid antibody syndrome; OAPS, obstetric antiphospholipid syndrome; PsA, psoriatic arthritis; LMWH, low molecular weight heparin; CDC, Centers for Disease Control and Prevention; cASA, low dose aspirin; SGA, small for gestational age; AGA, adequate gestational age; LGA, large for gestational age; W, weeks of gestation; PFO, patent foramen ovale; CHB, congenital heart block.

activation, and calcium signaling. These effects impact several immune system processes, collectively reducing the production and release of pro-inflammatory cytokines (1).

HCQ, in APS, shows pleiotropic immunomodulant and protective effects through multiple pathways; HCQ can reduce the binding of the antiphospholipid antibodies (aPL) to the syncytiotrophoblast, restoring the expression of annexin A5 which has an anticoagulant effect (2) and antagonising aPL by the inhibition of trophoblast migration, invasion, and differentiation, even if partially (3). A reduction of antibody production was also demonstrated by a study showing a gradual decrease in the levels of circulating aPL in antiphospholipid syndrome (APS) during pregnancy (4, 5).

Key mechanisms include endothelial cell activation, where aPL bind to endothelial cells and trigger a pro-thrombotic state. This state is reinforced by the activation of monocytes, platelets, and neutrophils, often involving complement activation (6). Cellular activation in APS involves the binding of aPLs to specific receptors within lipid rafts, specialized microdomains in the cell membrane that trigger signal transduction (7). Gender differences have also been linked to APS outcomes, with research indicating a correlation between gender-specific immune responses and clinical manifestations in APS patients (8).

Moreover, its safety in pregnancy has been addressed in numerous studies (9–23). Studies by Parke et al., who examined SLE patients who received HCQ, revealed no association between its use and congenital abnormalities (11). In addition, they highlighted the beneficial effect of HCQ during pregnancy in alleviating skin lesions (9, 11). The 2020 American College of Rheumatology (ACR) recommends HCQ administration to all pregnant women with SLE (Systemic Erythematosus Lupus) if possible (15). Furthermore, several studies have shown that maternal use of HCQ is associated with decreased disease activity and lupus flares and reduced cardiac and cutaneous manifestations of neonatal lupus (13, 14). Other studies have presented the benefits of HCQ in lowering the risk of adverse pregnancy outcomes in patients with SLE (16–20). In recent years, larger literature surveys have also concluded that antimalarial HCQ has to be preferred over chloroquine (21). HCQ is also preferred to Azathioprine (AZA) to control disease activity during pregnancy in patients with SLE because of the association between AZA and the increased risk of childhood infections (22). HCQ is safe during breastfeeding and is present in the breast milk of women undergoing treatment since the level ingested by breastfed infants is less than 0.2 mg/kg/day, which is a small fraction of the adult therapeutic dose of 5 mg/kg/day, as the American Academy of Ophthalmology recommends (23), it unlikely causes toxic effects (24).

Given the increasingly widespread use of HCQ during pregnancy, our study aimed to observe the pregnancy outcome and the postnatal health in infants born to mothers with systemic autoimmune rheumatic diseases, treated or not with HCQ.

Materials and methods

This retrospective observational cohort study was conducted at IRCSS-Policlinico "A. Gemelli" in Rome, from 2000 to 2020.

Women included in the study suffered from different systemic autoimmune rheumatic diseases: Systemic Erythematosus Lupus (SLE), Antiphospholipid Syndrome APS, Rheumatoid Arthritis (RA), Primary Sjogren's Syndrome (pSjS), Systemic Sclerosis (SSc), Undifferentiated Connective Tissue Disease (UCTD), Antiphospholipid Antibody positivity with non-criteria manifestations (aPL). Pregnancy and delivery data were collected from delivery room records; a telephone follow-up questionnaire was subsequently performed to describe the long-term pediatric outcome.

A total of 312 pregnancies were considered, 309 singleton and 4 twin pregnancies, which were excluded from statistical analysis in the birth weight and birth weight percentile indicators. Among all pregnancies, 16 spontaneous abortion and 3 intrauterine deaths occurred, and 2 cases were lost to follow-up. Complete data for follow-up were obtained in 182 cases. Patients were divided into two groups: women who took HCQ (400 mg/day) during pregnancy ($n = 135$ pregnancies) (HCQ group) and women ($n = 177$ pregnancies) who did not take HCQ during pregnancy (non-HCQ group).

The distribution of the different Rheumatic Diseases among enrolled patients is presented in Figures 1a,b according to the group.

All women in the study underwent clinical evaluation during pregnancy, and anamnestic, laboratory, and therapy data were collected retrospectively.

The anamnestic data included: patients' age at delivery, HCQ therapy taken during pregnancy and pre-conception, and any associated therapies [low-dose Aspirin, Low Molecular Weight Heparin (LWMH), Corticosteroids].

Delivery data were collected through the delivery room records at Policlinico "A. Gemelli" and, if patients had delivered elsewhere, by telephone questionnaire. Data included: mode of delivery (vaginal delivery or cesarean section); gestational age at the time of delivery; neonatal weight and weight percentile related to gestational age calculated according to Italian population curves (25); Apgar score at 1 and 5 min and admission to the neonatal intensive care unit.

Follow-up data included children's age (in months); weight and height with their percentiles calculated according to CDC (26) growth curves; exclusive maternal breastfeeding and its duration; regularity of vaccinations; and presence of diseases such as recurrent upper respiratory tract infections (≥4 episodes/year), gastrointestinal diseases, allergic diseases, atopic dermatitis, anaemia, cardiac diseases, visual impairment, hearing impairment, neurobehavioral developmental disorders, particularly language, and presence of congenital malformations.

Among the women in HCQ group, $n = 79$ cases completed the telephone questionnaire, while in non-HCQ group $n = 103$ cases completed the questionnaire; the remaining cases were lost due to: non-traceability by phone, language barrier, and refusal. In the following flow chart, the distribution of the excluded cases is shown.

Statistical analysis

The appropriate statistical tests, parametric and nonparametric (Student's or Mann-Whitney's *t*-test, al X2 or Fisher's test), were

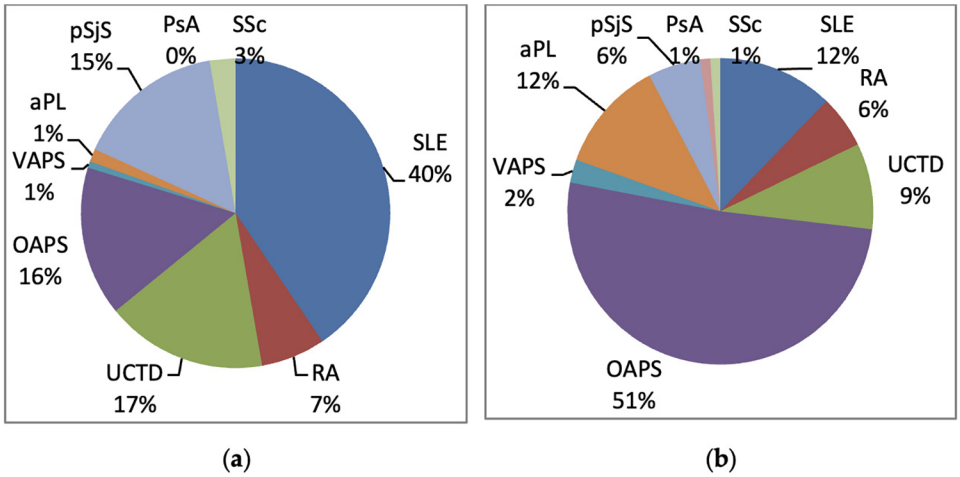

FIGURE 1
Distribution of autoimmune diseases in the two groups: **(a)** HCQ group; **(b)** non-HCQ group. aPL, antiphospholipid antibody positivity (aPL); VAPS, vascular antiphospholipid syndrome; OAPS, obstetric antiphospholipid syndrome; PsA, psoryatic arthritis; pSjS, primary Sjogren's syndrome; RA, rheumatoid arthritis; SLE, systemic erythematosus lupus; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

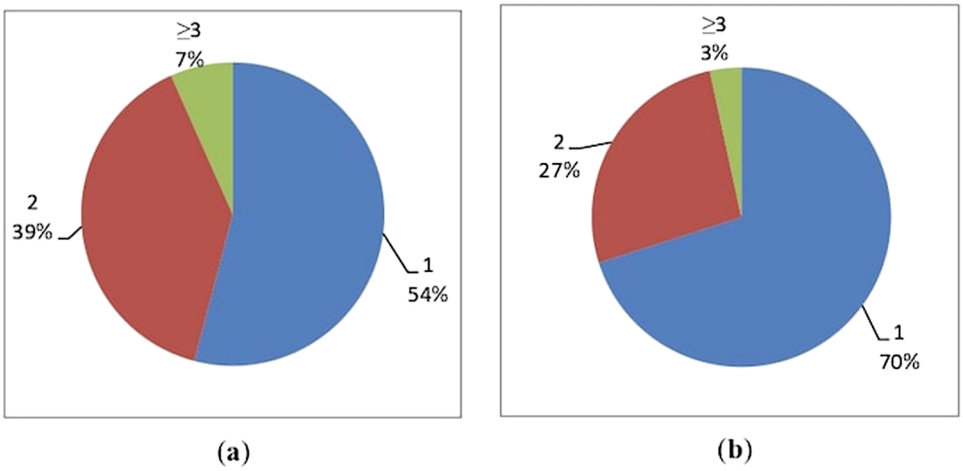

FIGURE 2
Distribution of associated autoimmune diseases in the two groups: **(a)** HCQ group; **(b)** non-HCQ group.

used to analyse the comparison between variables among the two groups of patients. Multivariate logistic regression was performed to confirm the association between postnatal health (presence/absence of disease) and the mother's use of HCQ during pregnancy. The analysis has been corrected with confounding factors such as birth weight, birth weight percentile, gestational week at delivery, and the mother's age at delivery (Supplementary Table S1).

Results with $p < 0.050$ were considered statistically significant.

Results

Women in the non-HCQ group were affected by a single autoimmune disease with a higher prevalence than women in the HCQ group (70% vs. 54%, p-value of 0.0045) (Figures 2a,b; Table 1). Accordingly, women in the HCQ group had a higher prevalence of multiple associated autoimmune diseases (39% vs. 27% in the non-HCQ group, with a p-value of 0.0015 (Figures 2a,b; Table 1).

Other drugs taken during pregnancy

The intake of additional therapies besides HCQ in these high-risk pregnancies has been investigated, as shown in Figure 3.

We found that Low dose Aspirin (100 mg, C-ASA) was taken by 74% of women in the HCQ group and 69% of women in the non-HCQ group ($p = 0.3364$). In addition, glucocorticoids were taken in 35% and 26% of cases, respectively ($p = 0.1247$). Regarding the

TABLE 1 Difference in distribution of associated autoimmune diseases between the two groups.

Presence of autoimmune diseases	HCQ	non-HCQ	*p*-value
1 pathology	54%	70%	**0.0045***
2 pathologies	39%	27%	**0.0015***
≥3 pathologies	7%	3%	0.1934

*and bolded values indicate a statistically significant result.

intake of Low molecular weight heparin (LMWH), its use was very similar in the two groups ($p = 0.0857$). All differences were not statistically significant, meaning that the other drug intake did not influence the comparison between the two groups.

Despite the high number of patients with SLE, in our study population, we didn't report a high percentage of women who used Azathioprine in pregnancy. We reported 3 patients in the HCQ group and 3 patients in the non-HCQ group, but two of them were lost at follow-up due to non-traceability by phone. For this reason, we did not add it to the figure of additional therapies in Figure 3.

HCQ trend over time

In our study population, the trend of HCQ intake over time was investigated, and we noticed an increasing use of this drug in the last two decades.

As shown in Figure 4, the prescription of HCQ over time has increased from 24% (years 2000–2004) to 59% in the last 5 years.

Obstetrical outcomes

Obstetric outcomes of the two groups are shown in Table 2.

In HCQ group the mean maternal age at delivery was 34 years (SD 4.56), 106 live births, 10 spontaneous abortions, and 2 intrauterine deaths were recorded; the number of vaginal deliveries was 56, compared with a lower number (50) of Caesarean sections; the gestational age at delivery was 37.33 ± 2.32 weeks (mean ± SD). The number of infants born <37 weeks' gestation who were classified as "late preterm" was 23%, while the "early preterm" infants born <34 weeks were 7%.

In non-HCQ group, the mean maternal age was 35 years (SD 6.23); 155 live births, 6 spontaneous abortions and 1 intrauterine death were recorded; the number of vaginal deliveries was 77 and of Caesarean sections 78, thus accounting for 50% of cases; the mean week at delivery was 37.77 ± 2.35 (mean ± SD). The "late preterm" rate was 17%, while the "early preterm" rate was 5%.

All the obstetrical parameters investigated were very similar in the two groups.

Multivariate logistic regression confirmed the association between lower maternal age and the use of HCQ (Supplementary Table S1).

Neonatal outcomes

Regarding neonatal outcomes, in the HCQ group we observed a mean birth weight of 2,838.46 ± 591.48 g (mean ± SD); the rate of low birth weight (<2,500 g) was 16%. In comparison, the mean birth weight in the non-HCQ group was 2,964.14 g ± 563.22 (mean ± SD); the rate of low birth weight (<2,500 g) was 17%. Birth weight resulted significantly different between the two groups (Table 2) even if multivariate logistic regression did not confirm this association (Supplementary Table S1).

The percentage of infants with percentile <10th, classified as SGA (Small for Gestational Age, WHO Definition) (26, 27) was very similar in the two groups (7% vs. 10%); similar results were found for infants >90th percentile, classified as LGA (Large for Gestational Age, WHO definition) (27, 28), (2% vs. 4%) (Table 2).

The Apgar index below 5 at 1′ and at 5′ was not different in the two groups.

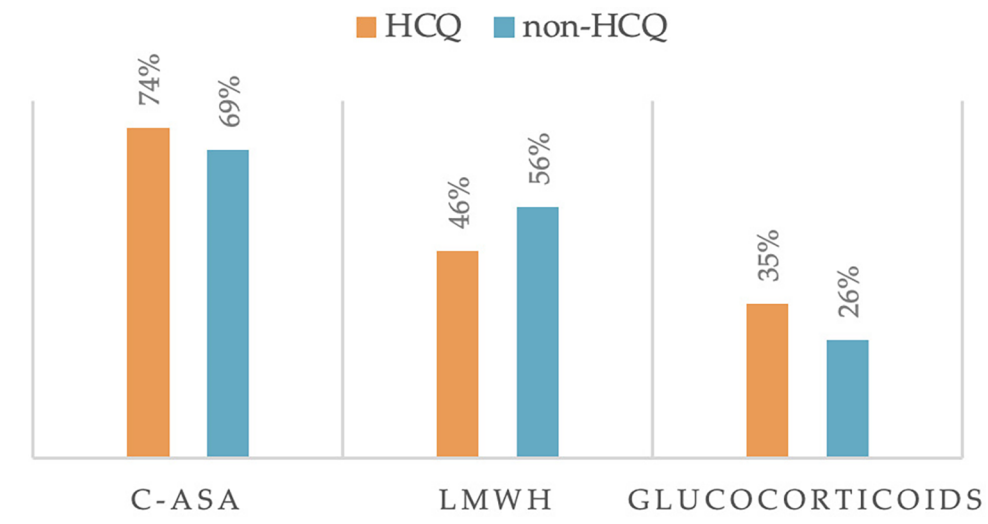

FIGURE 3
Other treatments taken during pregnancy (C-ASA, low dose aspirin; LMWH, low molecular weight heparin).

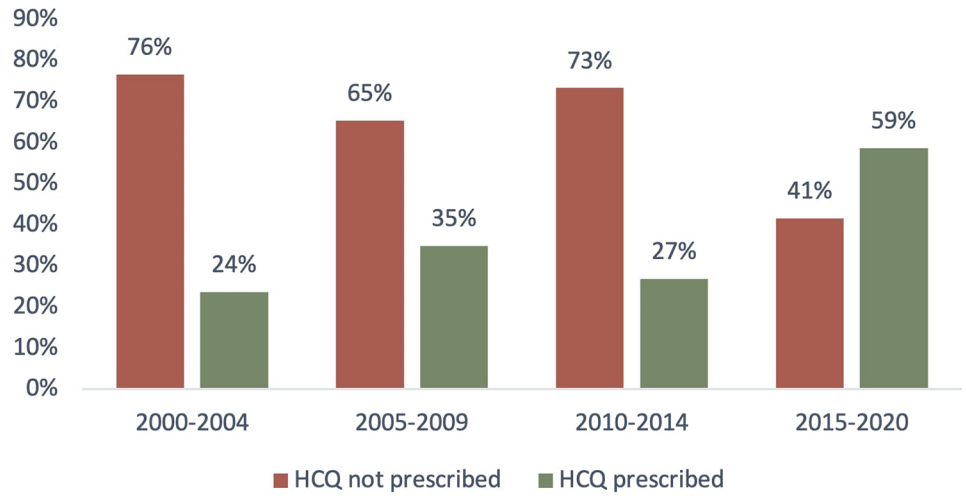

FIGURE 4
HCQ trend over time from 2000 to 2020.

TABLE 2 Obstetrical and neonatal outcomes.

	HCQ				non-HCQ				*p*-value
	N	%	Mean	SD	*N*	%	Mean	SD	
Age at birth	–	–	34	4.56	–	–	35	6.23	0.090
Vaginal delivery	56	53%	–	–	77	50%	–	–	0.720
Caesarean delivery	50	47%	–	–	78	50%	–	–	0.210
Gestational age at birth (w)	–	–	37.33	2.32	–	–	37.77	2.35	0.144
Late preterm (<37 w)	25	23%	–	–	27	17%	–	–	0.443
Early preterm (<34 w)	8	7%	–	–	8	5%	–	–	0.576
Birth weight	–	–	2,838.46	591.48	–	–	2,964.14	563.32	**0.040***
Low birth weight (<2,500 g)	17	16%	–	–	26	17%	–	–	0.594
Birth weight percentile	–	–	45.32	24.44	–	–	46.63	26.50	0.216
SGA (<10 pc)	8	7%	–	–	15	10%	–	–	0.393
AGA	97	91%	–	–	134	86%	–	–	0.441
LGA (>90 pc)	2	2%	–	–	6	4%	–	–	0.290
Apgar at 1′ <5	4	5%	–	–	2	4%	–	–	0.242
Apgar at 5′ <5	0	0%	–	–	1	2%	–	–	0.727

w, weeks; SGA, small for gestational age; AGA, adequate for gestational age; LGA, large for gestational age, WHO definition (26, 27).
*and bolded values indicate a statistically significant result.

Pediatric outcomes

Pediatric outcomes are shown in Tables 3, 4.

Telephone follow-up questionnaires on children showed the following results: in HCQ group, data were collected from $n = 79$ children, 35 boys and 44 girls, while the non-HCQ group included $n = 103$ children, 55 boys and 48 girls. Mean age at follow-up resulted different between the two groups, being significantly higher in the non-HCQ group. We attributed this difference to the fact that HCQ use increased over time (as described in Figure 4), and the older children of the non-HCQ group came from those pregnancies where HCQ was not common.

Regarding the children's health status, in the HCQ group 15% of the cases suffered from recurrent upper airway diseases, 9% from gastro-intestinal diseases, 22% suffered from allergic diseases and 18% had atopic dermatitis; 1% were anaemic, 8% had cardiological problems, including 3 cases of Patent Foramen Ovale (PFO), 1 case of Congenital Heart Block (CHB), 2 cases of patency of Botallo's duct; 22% had visual impairment (4 cases of myopia, 1 of astigmatism, 4 of hypermetropia, and 8 cases of mixed disorders) while none of them had hearing deficits; 13% had neurodevelopmental disorders, 4% delayed or impaired speech development, and 5% congenital defects.

In the non-HCQ group, 24% of cases presented recurrent respiratory infections, 13% gastrointestinal diseases and 26% allergies; 20% had atopic dermatitis, 8% anaemia and 9% cardiological problems (7 cases of POF and 2 cases of electrical conduction abnormalities); 24% had visual impairment (9 cases of myopia, 6 cases of astigmatism, 3 cases of hypermetropia and 7 cases of mixed disorders) and none with hearing, while 9% had neurobehavioral developmental disorders and in particular 4% speech deficits; finally, 7% of them had congenital defects.

TABLE 3 Pediatric outcomes.

	HCQ group				non-HCQ group				*p*-value
	N		Mean	SD	*N*		Mean	SD	
Age (months)	–	–	77.41	77.57	–	–	98.94	69.77	**0.012***
Males	35		–	–	55		–	–	0.235
Females	44		–	–	48		–	–	0.235
Weight (kg)	–	–	24.70	18.25	–	–	29.86	17.71	**0.028***
Weight percentile	–	–	62.19	28.81	–	–	52.93	29.66	**0.048***
Height (cm)	–	–	110.20	32.16	–	–	125.67	32.23	**0.001***
Height percentile	–	–	61.19	30.19	–	–	60.19	29.02	0.489
Breastfeeding	48	62%	–	–	63	62%	–	–	1.000
Breastfeeding time (months)	–	–	9.32	8.34	–	–	9.08	6.67	0.426

*and bolded values indicate a statistically significant result.

TABLE 4 Pediatric long-term outcomes.

	HCQ group *n* = 79		non-HCQ group *n* = 103		*p*-value
	N	%	*N*	%	
Recurrent upper airways infections (≥4 episodes/year)	12 (10)	15%	25	24%	0.2608
Gastro-intestinal diseases	7	9%	13	13%	0.4804
Allergies	17	22%	27	26%	0.4899
Atopic dermatitis	14	18%	21	20%	0.7071
Anemia	1	1%	8	8%	0.0798
Cardiac diseases	6	8%	9	9%	1.0000
Visual impairment	17	22%	25	24%	0.7244
Hearing impairment	0	0%	0	0%	1.0000
Neurodevelopmental impairment	10	13%	9	9%	0.4661
Speech impairment	3	4%	4	4%	1.0000
Malformations	4	5%	7	7%	0.8631
With any 1 pathology	18	23%	38	37%	0.0518
With any 2 pathologies	14	18%	16	16%	0.5566
With any ≥3 pathologies	16	20%	23	22%	0.7133
Without pathologies	**32**	**41%**	**26**	**25%**	**0.0368***

*and bolded values indicate a statistically significant result.

In comparison, children in the non-HCQ group showed a slightly higher prevalence of all these disorders, but the difference did not reach statistical significance.

When the children were divided into three groups (distinguishing those with no pathologies from those with 1, 2, or ≥ 3 pathologies), 40% of the children in the HCQ group did not suffer from any pathology vs. 25% of the children in non-HCQ group. This difference was statistically significant with a *p*-value of 0.0368 (Table 4). Multivariate logistic regression confirmed the association between the mother's use of HCQ and the absence of disease in the children when correcting with other factors, possibly affecting the health of the baby, such as birth weight and birth weight percentile, week of delivery, modality of delivery, age of the mother at delivery ($p = 0.008$).

Discussion

We analysed retrospectively a large sample of pregnant women complicated by the presence of systemic autoimmune rheumatic diseases.

HCQ has been gradually implemented in our Center over the years, due to improved knowledge about the safety and benefits of its use in pregnancy and lactation (10, 18, 20). As expected, therefore, in our results we confirm that the births throughout the most recent years occurred in pregnancies with wider use of HCQ.

In addition, we observed that women with multiple comorbidities had a higher prevalence of HCQ use compared to women suffering from a single autoimmune disease.

Regarding pregnancy outcome, we found a high rate of live births, with a low occurrence of fetal losses. In part, this can be explained by the fact that women with early-stage miscarriages did not come under our observation and, therefore, do not appear in this case history; another possibility is that the management of systemic autoimmune diseases in pregnancy has been improved over the years. Most obstetric outcome indicators were very similar in the two groups, such as the week of delivery, the birth weight percentile, the rate of low birth weight, and the number of preterm births.

In our opinion, the similar pregnancy outcome in the two groups supports the beneficial effect of HCQ during gestation. In fact, literature data suggest that patients with multiple medical conditions have less favourable pregnancy outcomes (29).

On this topic, a recent review by D'Ippolito et al. offers a thorough exploration of APS in pregnancy, delving into both well-established and novel mechanisms by which APS leads to obstetric complications. At the core of APS pathogenicity are aPL, which disrupt normal placental function by targeting trophoblast cells. This leads to placental thrombosis, inflammation, and impaired angiogenesis, causing adverse outcomes like recurrent miscarriages, fetal growth restriction, and preeclampsia (30). Moreover, further mechanisms are emerging for the identification of additional specificities and laboratory tests in those patients defined as seronegative (31).

Considering postnatal health, data on infants' follow-up was obtained through a telephone questionnaire. At follow-up, the children suffered from a substantial number of medical conditions: allergic diseases, atopic dermatitis, and visual impairment were the most represented. Our main finding was emphasized in the follow-up analysis, showing that infants in the HCQ group were disease-free at a significantly higher rate than those in the non-HCQ group. This observation suggests a potential role for HCQ in improving pregnancy outcomes and promoting infant health. Notably, this finding aligns with existing literature, which highlights HCQ benefits in improving live birth rates, reducing preterm births, and lowering the risk of neonatal complications such as cutaneous lupus and congenital heart block (32). These effects are due to the ability of HCQ to reduce inflammation, inhibit cytokine release, and modulate the immune environment in ways that may benefit fetal development and neonatal outcomes (32). The absence of an increased incidence of childhood infections in the HCQ group is particularly intriguing. This addresses an important safety concern regarding prenatal drug exposure and supports HCQ profile as a safe therapeutic option during pregnancy. By contributing to the growing body of evidence on HCQ exposure in pregnancy, our findings provide reassurance to clinicians and patients about its use in managing conditions such as SLE, Sjogren Syndrome and APS in pregnant women.

The present study has some limitations, as the absence of a control group from a general obstetric population limits our ability to identify the underlying causes of the high rate of observed medical conditions in infants. Moreover, incomplete data on NICU admissions prevented its inclusion in the statistical analysis, despite its potential value as a key indicator of neonatal health for future exploration. Additionally, the monocentric and retrospective design, along with the substantial number of cases lost to follow-up, further constrain the study's scope. Future research with a broader, multicentric and prospective approach is essential to generate more robust, long-term data. Moreover, further studies are needed to elucidate the mechanisms by which HCQ might influence fetal immune development and protect against disease manifestations in childhood.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethical Committee of Fondazione Policlinico Universitario A. Gemelli, Rome. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

VM: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. FR: Data curation, Software, Validation, Writing – original draft. MD: Investigation, Visualization, Writing – review & editing. SB: Investigation, Writing – original draft. AS: Visualization, Writing – review & editing. AL: Resources, Supervision, Validation, Writing – review & editing. EG: Formal analysis, Writing – review & editing. SD: Conceptualization, Resources, Writing – review & editing. CG: Resources, Software, Writing – review & editing, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer GR declared a shared affiliation with the authors VM and CG to the handling editor at the time of review.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/flupu.2025.1480867/full#supplementary-material

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A holistic approach is needed for women with an inflammatory arthritis in the different phases around pregnancy; the results of the CAPRI study

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Introduction: Women with inflammatory arthritis (IA) face significant challenges throughout preconception, pregnancy, and postpartum phases, including concerns about disease management and medication safety. The Reproductive Rheumatology care pathway at Erasmus University Medical Center integrates specialized care from rheumatologists and specialized nurses to address both medical, nursing, practical and emotional needs during these phases. This study evaluates patient satisfaction, identifies unmet needs, and explores opportunities for enhancing support within this integrated care model.

Methods: This was a cross-sectional study. We designed a customized questionnaire for women 18 years and older who were treated following the Reproductive Rheumatology care pathway and had given birth between 2019 and 2021. These women were invited to fill in the questionnaire. The survey assessed satisfaction with care, challenges experienced, and information needs across preconception, pregnancy, and postpartum phases. Descriptive statistics and paired *t*-tests were used for data analysis.

Results: Participants reported high satisfaction with care, rating rheumatologists an average of 8.8/10 and specialized nurses 9.2/10. While 78.9% experienced no major issues, some faced problems such as managing disease flares and difficulties around conception. Information needs varied by phase: preconception needs focused on medication safety and fertility, while pregnancy and postpartum concerns included disease management and emotional support. Specialized nurses were pivotal in offering personalized care and practical advice.

Conclusion: The integrated Reproductive Rheumatology care pathway effectively supports women with IA through their reproductive journey. Despite high satisfaction, improvements could be made in personalized care and addressing challenges related to confidence and help acceptance. Future research should investigate the long-term impact of such care pathways on reproductive outcomes and patient well-being.

KEYWORDS

inflammatory arthritis, pregnancy, reproductive rheumatology, patient satisfaction, specialized nurse, integrated care pathway

Introduction

Recent advancements in inflammatory arthritis (IA), such as early diagnosis, prompt initiation of disease-modifying antirheumatic drugs (DMARDs), including tumor necrosis factor (TNF) inhibitors, and a treat-to-target (T2T) approach aiming for remission, have led to improved patient outcomes and quality of life (1). Nonetheless, for women diagnosed with IA and a wish to conceive (or a pregnancy) represents a challenge because it is known that IA significantly impacts fertility and pregnancy outcomes (2, 3). Specialized care remains crucial to navigate the complexities around conception, pregnancy, and the postpartum phase (4).

At the Department of Rheumatology at Erasmus University Medical Center, women diagnosed with IA who wish to conceive (or are already pregnant) have access to an established comprehensive "Reproductive Rheumatology" care pathway. A care pathway is a multidisciplinary plan that outlines the essential steps in the care of patients with a specific clinical problem, aimed at improving the quality and coordination of care (5). The Reproductive Rheumatology care pathway at Erasmus University Medical Center combines consultations by rheumatologists and specialized rheumatology nurses (RNs). When indicated other specialists, such as gynecologists, will be involved.

In short, at each visit patients receive specialized care tailored to their reproductive goals from both a rheumatologist and a RN, addressing needs from preconception through six months post-delivery. The rationale behind our care pathway stems from our experience that in addition to medical consultations by rheumatologists, which mainly focus on disease and treatment strategies, complementary support is needed (6). The RNs play a pivotal role in addressing these holistic aspects of care, including emotional well-being, sexual health, work-life balance, and practical aspects of parenthood. Nursing consultations also include patient educational opportunities in relation to any concerns regarding pregnancy and rheumatic disease. The purpose of this coordinated approach between rheumatologists and RNs is to provide seamless support throughout every phase of the patient's reproductive journey, optimizing patient care outcomes.

Our primary objective was to evaluate patient satisfaction with our integrated care pathway. As secondary objectives we aimed to describe the problems patients experience during the care pathway process and to identify the unmet needs that were not covered by the care pathway. Ultimately, the results of this study can be used to determine the most effective timing and delivery of counseling information and to enhance the support provided to women with inflammatory arthritis throughout their journey into motherhood.

Methods

Patient population and data collection

We designed a customized questionnaire for women aged 18 years and older who had given birth between September 2018 and April 2021. These women, treated following the Reproductive Rheumatology care pathway at the Department of Rheumatology at Erasmus University Medical Center, were invited to fill in the questionnaire online. A reminder was sent to non-responders two months after the initial invitation.

Questionnaire development

The customized questionnaire was structured into sections tailored to different phases around pregnancy: preconception, pregnancy, and postpartum. It covered topics such as family planning and family size, parenthood, social support received during these phases, and counseling provided by the care pathway team. Participants were also invited to provide suggestions and personal feedback through free-text options.

Additionally, the questionnaire included statements regarding women's perspectives on preconception, pregnancy, postpartum, parenthood, and support. Participants were asked to rate their agreement to these statements on a scale from "totally disagree" to "totally agree" (Likert scale). Lastly, participants rated their satisfaction with rheumatologists and RNs on a scale from 1 (lowest) to 10 (highest).

Statistical analysis

Data analysis was performed using STATA version 17. Descriptive statistics were used to summarize demographic characteristics, satisfaction scores, and responses to questionnaire items. Categorical variables are presented as frequencies and percentages, while continuous variables are reported as means with standard deviations or as medians with interquartile ranges, depending on their distribution.

To assess differences in satisfaction scores between rheumatologists and specialized nurses, paired *t*-tests were conducted. Chi-square tests or Fisher's exact tests were used to evaluate associations between categorical variables, such as problems encountered during different pregnancy phases and their resolutions.

All statistical tests were two-sided, and *p*-values less than 0.05 were considered statistically significant.

Ethics

This study was reviewed by the Erasmus University Medical Center ethics committee was deemed in compliance with the Helsinki declaration. All patients were 18 years or older, had a good understanding of the Dutch language and provided their informed consent by ticking a box on the front page of the online questionnaire.

Results

Out of 181 women invited, 95 responded, resulting in a completion rate of 52.5%. The demographic characteristics of participants are presented in Table 1.

Satisfaction with care

The results indicate high satisfaction among women with the care they received. They rated rheumatologists with an average score of 8.8/10 and specialized nurses with an average score of 9.2/10. Furthermore, 96% of participants ($n = 80$) reported consistent information across healthcare providers.

Problems experienced during the care pathway

Seventy-five women (78.9%) did not experience any problems during the preconception, pregnancy, or postpartum phases. Among the problems reported by the remaining 18 women (19.4%), issues included managing disease flares ($n = 13$), difficulty conceiving ($n = 4$), lack of collaboration between specialists ($n = 2$), and other non-rheumatological issues ($n = 1$). Twelve women successfully resolved their problems with or without assistance from the care pathway team, while six women (6.4%) were unable to resolve their issues (pain/disease activity ($n = 3$), non-IA-related issues ($n = 2$) and concerns about safety of medication during pregnancy ($n = 1$).

TABLE 1 Participants demographic and clinical characteristics at time of completing questionnaire.

	N = 95
Age, mean (range)	34.1 (26–46)
Diagnosis, *n* (%)	
Rheumatoid arthritis	39 (41)
Psoriatic arthritis	19 (20)
Spondyloarthritis	18 (19)
Juvenile idiopathic arthritis	16 (17)
Other immunologic disease	3 (3)
Disease duration, mean (SD)	
Rheumatoid arthritis	10.3 (6.5)
Psoriatic arthritis	6.6 (4.0)
Spondyloarthritis	6.9 (4.9)
Juvenile idiopathic arthritis	23.6 (5.3)
Other immunologic disease	7.0 (4.2)
Child(ren)	
Number, mean (range)	1.5 (1–3)
Age youngest child (months), mean (SD)	14.0 (7.6)
First child, *n* (%)	58 (61)
Housing situation, *n* (%)	
With partner and with children at home	86 (90.5)
Without partner and with children at home	1 (1)
Not specified	8 (8.5)
Education*	
Bachelor degree or higher, *n* (%)	58 (67)
Work*	
Paid work	
- *n* (%)	76 (87)
- Hours per week, mean (range)	27 (8–40)
Incapacitated for work (partially or complete), *n* (%)	6 (7)

*$n = 87$.

Additionally, we examined whether being a first-time mother influenced the problems experienced. Of the six women who had unresolved issues, five were expecting their first child (data not shown).

Information needs per phase (preconception, pregnancy and postpartum)

During the preconception phase, participants primarily expressed a need for information about medication (Figure 1). They also needed details on how the disease and medication affect fertility and pregnancy, as well as general advice on lifestyle and nutrition. During pregnancy and after childbirth, the focus shifted to understanding the progression of the disease during these phases and practical advice on topics like breastfeeding, ergonomic tips and work-life balance. During the postpartum phase, more women expressed a desire for support from women in similar situations and other healthcare professionals (Figures 2a, b).

Statements evaluation

Participants responded to statements regarding their perspectives on pregnancy, postpartum, parenthood, and support. Notably:

- "Through the information from the rheumatology care team, I gained more knowledge and understanding about, pregnancy, and the postpartum phase." 88% of the women agreed or totally agreed with this statement.
- "I have difficulty accepting help." Responses varied widely, with 50.6% indicating agreement or total agreement.
- "Through the rheumatology care team, I have become more confident about, pregnancy, and the postpartum phase." Responses showed a positive trend, with 67.8% agreeing or totally agreeing.

Discussion

Our study explored the experiences and expectations of women with IA accessing specialized care during pregnancy within the Reproductive Rheumatology care pathway. Overall, participants expressed high satisfaction with the integrated care provided by the care pathway, including rheumatologists and specialized nurses, highlighting the pathway's efficacy in meeting the complex needs of women with IA throughout their reproductive journey.

Challenges encountered, such as managing disease flares and difficulties with conception, were reported by a subset of participants. However, with the support of the care pathway team, most issues were effectively managed, highlighting the accessibility and effectiveness of healthcare interventions in this setting. The finding that a majority of women with unresolved problems were expecting their first child may indicate additional challenges for first-time mothers.

Information needs varied significantly across different pregnancy phases. During the preconception phase, participants

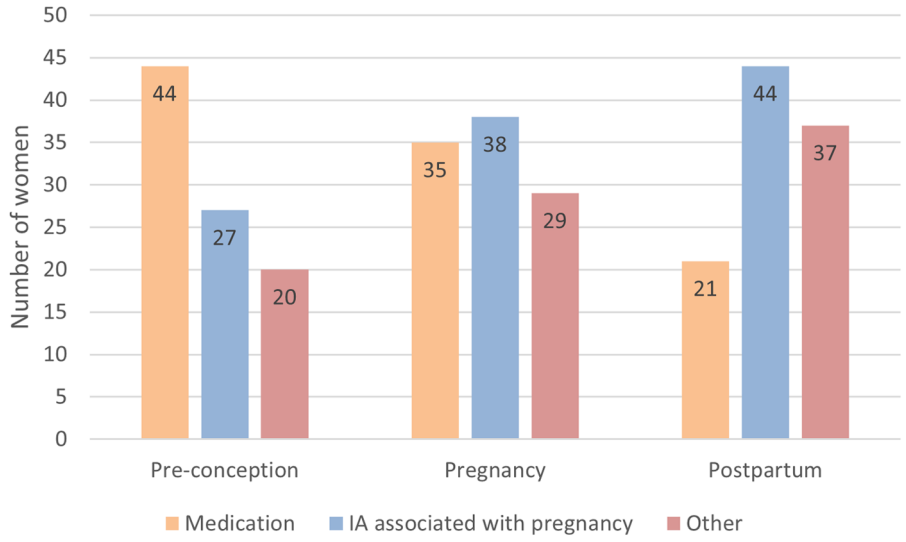

FIGURE 1
Topics women want to discuss in the different phases around pregnancy. *IA, inflammatory arthritis.

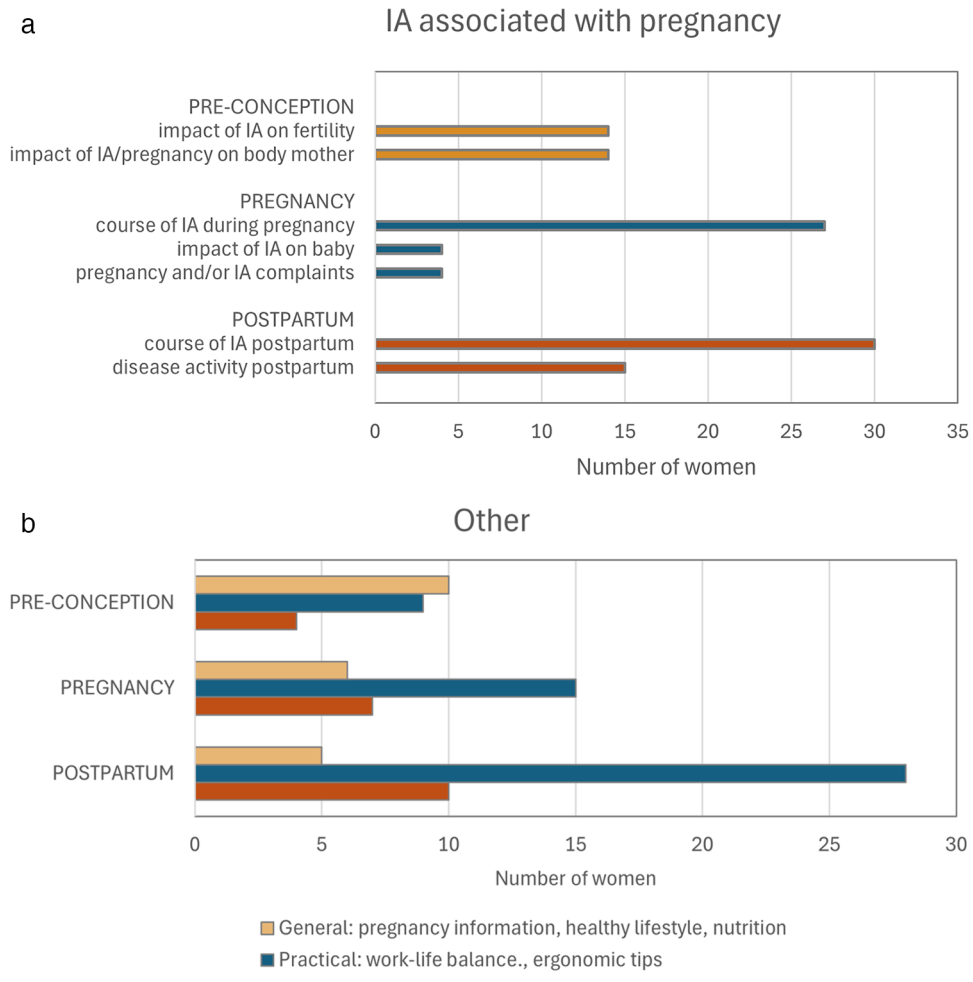

FIGURE 2
(a) Category "IA associated with pregnancy" specified. (b) Category "Other" specified.

sought guidance on medication safety, fertility, and hereditary considerations. In contrast, pregnancy and postpartum phases emphasized disease management, medication safety during breastfeeding, and overall well-being. Postpartum, there was also a strong desire for practical advice ergonomic tips, and shared experiences from other women.

Participants strongly endorsed the role of counseling provided by the care pathway team, reporting increased knowledge and confidence about, pregnancy, and postpartum care. However, challenges in accepting help and maintaining confidence were also noted, suggesting the importance of personalized support strategies tailored to individual needs.

Healthcare professionals should recognize that these factors can significantly influence a patient's overall well-being and should be integrated into clinical care. Additionally, it is important to encourage patients to feel comfortable seeking help, whether from healthcare providers, family, or their social circle. Creating a supportive atmosphere where patients feel empowered to ask for assistance is critical to improving both physical and emotional outcomes.

While our study benefited from a robust methodology, including a tailored questionnaire and high response rate, it is important to acknowledge limitations such as potential response bias, the retrospective nature of data collection and the use of a non-validated questionnaire. Future research could explore longitudinal outcomes and assess the sustained impact of interventions within similar specialized care pathways.

When comparing these findings to other studies on similar care pathways, our approach demonstrates the value of comprehensive integration between specialized nurses and rheumatologists, distinguishing it from traditional models that often lack coordinated care. For example, other studies have highlighted that fragmented care systems can leave patients feeling unsupported and overwhelmed (7, 8).

In contrast, our reproductive rheumatology model mitigates these issues by providing consistent, interdisciplinary, and holistic support throughout each phase of pregnancy. This includes flexible appointment scheduling, customized counseling, and a focus on psychological resilience, tailored to individual needs. These features not only improve patient confidence and acceptance of care but also contribute to enhanced outcomes and satisfaction. We believe these lessons could inform the development of more effective, patient-centered care pathways in the future.

In conclusion, our findings underscore the pivotal role of Reproductive Rheumatology care pathways in supporting women with IA through pregnancy. By addressing specific challenges and information needs, healthcare providers such as RNs can enhance the quality of care and outcomes for these women, ultimately improving their reproductive health and well-being.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Erasmus University Medical Center ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AS: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. HW: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ER: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. HS: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LK: Writing – original draft, Writing – review & editing. RD: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LP-G: Data curation, Formal Analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Altered hemostatic balance in favor of a procoagulant state in pregnant women with systemic lupus erythematosus

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Objectives: This study aimed to investigate hemostatic parameters in pregnant patients with systemic lupus erythematosus (SLE) in relation to the use of antithrombotic prophylaxis, preeclampsia (PE), and antiphospholipid antibody status.
Patients and methods: In total, 34 pregnant patients with SLE and 80 pregnant healthy controls (HC) without PE were included. Patients with SLE were sampled during the first and third trimester of gestation. We analyzed fibrinogen, D-dimer, and global hemostatic parameters including the overall coagulation potential (OCP), overall hemostatic potential (OHP), and the overall fibrinolysis potential (OFP). Fibrin structure was visualized using scanning electron microscopy.
Results: The median age of the patients with SLE was 33 (range 23–42) years and 31 (26–38) years in the HC. The median disease duration was 10 (range 0–26) years. All but two patients with SLE received prophylaxis with low-dose acetylsalicylic acid (LDASA) and 11 received low-molecular-weight heparin (LMWH). OCP and OHP were significantly increased in the patients with SLE compared to HC ($p < 0.01$). The levels of fibrinogen and D-dimer increased throughout the pregnancies in the patients with SLE, but no differences were found in the third trimester compared to controls. Among the patients treated with LMWH, OCP, OHP, and OFP were undetectable in two, both of whom were on high prophylactic dosage, and one developed PE. OCP, OHP, and OFP levels were not affected by low prophylactic doses of LMWH. Despite LDASA, preeclampsia occurred in four patients with SLE (12.5%); of whom two received a high prophylactic LMWH dose. Five of 32 (15.6%) patients had major bleeding complications at delivery. There were no thromboembolic complications.
Conclusions: In this pilot study, pregnant patients with SLE developed a hypercoagulable state throughout pregnancy, as demonstrated by the global hemostatic parameters OCP and OHP, except for two patients who were treated with a full dosage of LMWH. The alterations in the coagulation system in SLE pregnancy need to be further studied with the aim of optimizing treatment strategies.

KEYWORDS

systemic lupus erythematosus, pregnancy, anticoagulant treatment, preeclampsia, global hemostasis assay

Introduction

Systemic lupus erythematosus (SLE) predominantly affects women of reproductive age, constituting a significant gestational risk factor. Women with SLE are at increased risk of severe pregnancy complications, such as preeclampsia (PE), preterm delivery, fetal death, and several other adverse pregnancy outcomes (APOs) (1–4). Further, pregnancy can exacerbate disease manifestations leading to SLE flares and irreversible organ damage, contributing to considerable maternal morbidity (5–7).

Thromboembolic manifestations are common during SLE pregnancy, as shown by several studies (8–10). The underlying hemostatic disturbances during SLE pregnancy are poorly studied, despite the known propensity to develop a hypercoagulable state during the gestation period, as also shown in healthy women (11). Recently, in a study on the global hemostatic potential, we demonstrated enhanced coagulation and impaired fibrinolysis in healthy women suffering from PE during the third gestational trimester (12). As patients with SLE have an increased risk for PE development, we hypothesized that similar findings could contribute to adverse pregnancy outcomes in SLE pregnancy.

Antiphospholipid antibodies (aPL) and lupus nephritis (LN) significantly contribute to fetal and maternal complications and are known risk factors for the development of PE (13, 14). In addition, positivity for aPL further enhances the risk for thromboembolic complications during pregnancy (15). In a previous study, we demonstrated an increased risk of PE specifically in women with LN compared to patients with non-renal SLE (26 vs. 3%), regardless of the presence of concurrent antenatal flares (16).

This study aimed to investigate hemostatic variables in pregnant women with SLE in relation to the use of anticoagulant prophylaxis, aPL status, and development of thromboembolic complications and PE.

Patients and methods

In total, 34 pregnant patients with SLE followed between 2019 and 2022 at the Rheumatology Clinic, Karolinska University Hospital, were included in the study. All the patients fulfilled the American College of Rheumatology (ACR) criteria and/or the Systemic Lupus International Collaborating Clinics for SLE (17, 18). Patients older than 18 years of age with an SLE diagnosis prior to conception who were followed during pregnancy at the SLE outpatient clinic were included. Clinical and laboratory data were collected and the patients were sampled during the first (weeks 10–12, T1) and the third (weeks 32–34, T3) trimester of gestation for research purposes.

Thus, 22 of the patients had samples taken during T1, of whom 2 miscarried, 28 patients were sampled in T3, and 16 patients had samples taken at both study timepoints.

As a control population, 80 pregnant healthy controls (HCs) who had been sampled during T3 of gestation were included (12). HCs scheduled for routine prenatal care visits during T3 were included in the study. All HCs had uncomplicated pregnancies and had no history of cardiovascular disease (CVD), venous thromboembolism (VTE), or treatment with antithrombotic or anticoagulant drugs.

All the participants had given their oral and written consent to participate, and the study was performed according to the Declaration of Helsinki. The study was approved by the Swedish Ethical Review Authority (2021-02559) and the local Ethics Committee of Gynaecology and Obstetrics Clinic "Narodni Front," Belgrade, Serbia (24/5-1).

Clinical variables were retrieved from electronic medical records. This included age at conception, disease duration, occurrence of lupus nephritis (ever), ongoing immunosuppressing therapy, and a special focus on the use of anticoagulant therapy. The occurrence of secondary antiphospholipid syndrome (sAPS) defined according to the Sapporo criteria (19) was recorded.

We also retrieved data regarding disease activity 12 months before conception where active disease was defined as having a SLE Disease Activity Index 2000 (SLEDAI-2K) score >4 (20).

Blood sampling

Peripheral venous blood was collected in tubes containing clot activator or trisodium citrate. Serum and platelet-poor plasma (PPP) were obtained within 60 min of sampling by centrifugation at 2,000 g for 20 min at room temperature and then aliquoted and frozen at −80°C. The analyses of hemostatic parameters were performed at Karolinska Institutet, Department of Molecular Medicine and Surgery, Coagulation Laboratory.

Analysis of hemostatic parameters

Determination of overall hemostatic potential and turbidimetric parameters of fibrin clots in plasma

To assess overall hemostatic potential (OHP) in plasma, a modified assay described by He et al. was employed (21). The assay is based on the spectrophotometric registration of Absorbance (Abs) at 405 nm every 12 s for 60 min in recalcified plasma after the addition of a small amount of thrombin and tissue plasminogen activator (t-PA). Fibrin formation is calculated as the area under the curve (Abs-sum) and expressed as the OHP. Two additional parameters were also analyzed—overall coagulation potential (OCP), determined as the area under the fibrin aggregation curve obtained without the addition of t-PA, and the overall fibrinolytic potential (OFP), calculated as the difference between the two areas as OFP (%) = [(OCP − OHP)/OCP] × 100. The intra- and inter-assay coefficients of variation for OHP were 1.6% and 6.8% and for OCP were 1.2% and 5.7%, respectively. The reference range for OCP, OHP, and OFP was established at our laboratory and presented as 25th–75th percentile.

The turbidimetric curve for determination of OCP was used to assess fibrin clot density by the following parameters: "lag time,"

measuring clotting time as the time-point when exponential growth of the curve starts; "max absorbance," reflecting clot density calculated as the average value of three consecutive points where the curve reached a plateau; and the "slope," measuring the polymerization rate of fibrin (22).

Determination of clot lysis time

The turbidimetric curve for the determination of OHP was used for the calculation of clot lysis time (CLT) and was defined as the time from the midpoint of the clear-to-maximum turbid transition to the midpoint of the maximum turbid-to-clear transition.

To study the effects of thrombin activatable fibrinolysis inhibitor (TAFI) on CLT, a specific TAFI potato tuber carboxypeptidase inhibitor (PTCI) was added to plasma samples, to a final concentration of 50 µg/ml, and the OHP assay was performed. CLT was measured before and after PTCI addition and the difference (dCLT) was calculated.

Scanning electron microscopy of fibrin clots

The clots formed during fibrin generation were washed, fixed in 2.5% glutaraldehyde, and stored at 4°C. The specimens were analyzed in an Ultra 55 field emission scanning electron microscope (Carl Zeiss) and individual fiber thickness was measured as previously described (22). To visualize fibrin clots, two different magnifications were used, 1 µM and 300 nm, respectively.

Analyses of fibrinogen and D-dimer levels

Dade Thrombin Reagent Siemens, Germany, was used for the determination of fibrinogen concentration using the Caluss method in the patient group, while the modified Caluss method with Multifibren U reagent, Siemens, Germany, was used for measuring fibrinogen concentration in the control group. The INNOVANCE® (Siemens, Germany) D-Dimer Assay, a particle-enhanced immunoturbidimetric assay, was used for the quantitative determination of cross-linked fibrin degradation products (D-dimers).

Serology

Serologic analyses were performed in Clinical Immunology and Clinical Chemistry at the Karolinska University Hospital according to clinical routine. The panel for aPL assays comprised IgG and IgM isotypes for both anti-cardiolipin (aCL) and anti-beta2glycoprotein I (anti-beta2GPI) antibodies, and the functional lupus anticoagulant (LA) test. Anti-dsDNA antibodies were analyzed by immunofluorescence microscopy using *Crithidia luciliae* as the source of antigen.

Pregnancy outcome

Information regarding the development of PE or thrombotic or major bleeding events was retrieved from the medical records. PE was defined as gestational hypertension and new onset of proteinuria (≥300 mg/24 h) after 20 weeks of gestation (23). A major bleeding at delivery was defined as a hemorrhage of >500 ml in cases of vaginal delivery and >1,000 ml in C-section patients (24).

Statistics

Descriptive statistics was used for presentation of patient's characteristics as median (IQR). Fisher's exact test was used for testing continuous variables. The Mann–Whitney *U*-test was used for group comparisons and the results are presented as median (IQR). For comparison between two related groups, the Wilcoxon signed ranks test was used. Spearman's analysis was performed to examine correlations. For comparison between more than two groups, the Kruskal–Wallis test was computed. The *p*-value was significant if <0.05. Analyses were performed using the GraphPad program.

Results

The general characteristics of the patients and controls are presented in Table 1.

The median age at inclusion was 33 (range 23–42) years, and the median disease duration was 10 (range 0–26) years in the patients with SLE. The median age in the controls was 31 (26–38) years. In total, 29 patients (85%) were of Caucasian origin. None of the patients were smokers but one patient used smokeless tobacco (snuff). None of the patients developed gestational diabetes.

Furthermore, 20 of the patients were primiparous, 13 had one previous delivery, and 1 patient had two. One patient had a previous episode of hepatic vein thrombosis during a previous pregnancy and diagnosis of SLE/APS was established. Her pregnancy was medically terminated in the second trimester of pregnancy (here regarded as primiparous). Otherwise, there were no cases of PE during the previous pregnancies in the parous patients.

Three of 33 (10%) patients with available data were defined as having active disease the year before the pregnancy, of whom 1 developed PE. There was no association with active disease within 12 months of gestation and development of PE. Finally, 10/34 (29.4%) had a history of LN confirmed by a kidney biopsy in all but one case.

Treatment

Low-molecular-weight heparin (LMWH) was given in 11 cases. High-dose thromboprophylaxis was given twice daily to three patients and was guided by measurement of the nadir level of anti-factor Xa concentration according to clinical routines.

Eight patients received prophylactic LMWH once daily, the so-called low prophylactic dosage. Twenty-eight patients (82%) received hydroxychloroquine (HCQ) treatment and 32 (94%) low-dose acetylsalicylic acid (LDASA) (75 mg/day) during pregnancy. Ten patients were treated with prednisolone at a median dose of 5 mg/day (range 2.5–10). There was no statistical

TABLE 1 Baseline characteristics of pregnant patients with SLE and pregnant healthy controls.

	SLE all ($n = 34$)	SLE without PE ($n = 30$)	SLE with PE ($n = 4$)	p-value	HC without PE ($n = 80$)
Age, years, median (range)	33 (23–42)	33 (23–42)	34 (30–40)	NS	31 (26–38)
Disease duration years, median (range)	10 (0–26)	10 (0–26)	15.5 (3–26)	NS	NA
Primiparous, *n*	20	18	2	NS	45
Caucasian ethnicity, *n*	28	25	3	NS	80 (100)
SLEDAI score $\geq$ 4, 12 months prior to pregnancy, *n*	3/33	2/29	1	NS	NA
History of lupus nephritis, *n*	10	8	2	NS	NA
APS, *n* (%)	1	0	1	NS	NA
aPL carrier, *n*	7	5	2	NS	2 (2.5)
LDASA, *n*	32	28	4	NS	0
LMWH, *n*	11	9	2	NS	0
Major bleeding complications	5/32	4/28	1/4	NS	NA
Prednisolone, *n*	10	7	3	NS	NA
Dose of prednisolone[a], median (range)	5 (2.5–10)	5 (2.5–10)	5 (0–5)	NS	NA
Hydroxychloroquine, *n*	28	24	4	NS	NA
Azathioprine *n*	7	6	1	NS	NA
Cyclosporine-A	3	3	0	NS	NA
Antihypertensives	6	3	3		NA
Levotyroxin	5	5	0		

PE, preeclampsia; NA, not analyzed; APS, antiphospholipid syndrome; aPL, antiphospholipid antibodies; SLEDAI, SLE disease activity index; LDASA, low-dose acetylsalicylic acid; LMWH, low-molecular-weight heparin; NA, not applicable.
[a]Only in treated patients.

difference regarding the use of prednisolone when comparing PE and non-PE patients ($p = 0.16$). Ten of the patients (29%) were on immunosuppressing therapy, of whom seven received azathioprine and three cyclosporine-A (Table 1). Data on patients receiving LMWH are presented in Table 2.

Coagulation analyses

Data on coagulation variables were available in 22 patients in T1 and 28 in T3. In 16 cases, data was available in both T1 and T3. Of these 16 patients, 5 received LMWH prophylaxis.

Figure 1 presents the levels of coagulation parameters in 80 healthy pregnant women (HC) sampled during T3 and pregnant women with SLE in T1 and T3, while separate graphs show the same parameters in the 16 patients sampled in both T1 and T3.

There was a significant increase in fibrinogen and D-dimer levels along with the pregnancy stage ($p < 0.001$, respectively). Fibrinogen levels in T1 (median 4.06; IQR 3.6–4.5) were within the reference range (2–4.5 g/L), while D-dimer (median 0.34; IQR 0.26–0.59) was under the cut-off (<0.5 mg/L) in most of the patients (Figures 1A,B). In T3, both fibrinogen (4.65; IQR 4.5–5.5) and D-dimer levels (1.41; IQR 1.0–1.56) increased above the upper reference ranges in all patients, since these parameters are unaffected by anticoagulant treatment. A significant increase was seen in both fibrinogen and D-dimer levels in patients sampled at both T1 and T3 ($p < 0.01$ and $p < 0.001$, respectively).

The OHP assay detected two completely anticoagulated patients with undetectable levels, both treated with high prophylactic doses of LMWH (Figure 1C, LMWH patients marked in red). In all patients treated with low prophylactic doses of LMWH, OHP was within the reference range in T1 (88–158) and increased above the upper reference range in T3. In the patients with detectable OHP levels, there was a significant increase of OHP from T1 to T3 (155.7; IQR 146.2–174.2 vs. 211.8; IQR 171.5–246.7, $p < 0.01$). A significant increase was seen in patients sampled at both pregnancy timepoints ($p < 0.01$) (right panel of Figure 1C).

OCP was also undetectable in two patients, as described above. In most of the patients with detectable OCP levels, OCP was above the reference range (213–304) in both T1 and T3 and increased along with the pregnancy stage (387.6; IQR 333.2–414.7 vs. 407.1; IQR 372.3–444.2), however, the increase was not significant ($p = 0.15$) (Figure 1D).

OFP decreased significantly from T1 to T3 (59; IQR 52%–62% vs. 50; IQR 37%–57%, $p < 0.01$), while the levels remained within the reference range (45%–61%) in most of the patients (Figure 1E).

CLT increased from T1 to T3, though not significantly (1,490; IQR 1,310–1,710 vs. 1,630; IQR 1,400–1,960, $p = 0.2$) and within the reference range (1,180–1,850 s). There was no difference between CLT in the HCs (1,533; IQR 1,338–1,685) compared to CLT in the SLE pregnancies in T1 and T3 (Table 3).

Coagulation parameters in 28 patients sampled in T3 compared to 80 healthy controls

Table 3 displays the levels of coagulation parameters in 28 pregnant women with SLE sampled in the third trimester and in 80 healthy pregnant women during the same gestational stage.

Ten patients (of a total of 11) treated with LMWH were sampled in T3. As described above, in two patients with a high prophylactic dosage of LMWH, all the investigated coagulation parameters were undetectable, except for fibrinogen and

TABLE 2 Characteristics and complications in 11 patients treated with low-molecular-weight heparin.

Indication for LMWH	aPL, positivity	History of LN	LDASA	Dose of LMWH	OCP undetectable	PE	Major bleeding	Mode of delivery
aPL positivity and active LN	aCL IgG, B2GP-1 IgG	Yes	Yes	High prophylactic	No	Yes	Yes[a] attributed to uterus atonia	Vaginal
Three previous miscarriages	0	No	Yes	Prophylactic	No	No	No	C-section, planned
APS	aCL IgG, B2GP-1 IgG LAC	No	Yes	Full dose	Yes	Yes	No	Vaginal
Four previous miscarriages, previous aPL positivity	previously B2GP-1 IgG	No	Yes	Prophylactic	No	No	No	Vaginal
aPL positivity	aCL IgG + IgM, B2GP-1 IgG + IgM, LAC	No	Yes	High prophylactic	Yes	No	No	Vaginal
Previous miscarriage	LAC	Yes	Yes	Prophylactic	No	No	No	Vaginal, induced
aPL positivity	aCL IgG + IgM, B2GP-1 IgG + IgM, LAC	No	Yes	Prophylactic	No	No	No	C-section, planned
Previous pregnancy complication (diplopia), previous aPL	previously LAC	No	Yes	Prophylactic	No	No	No	Vaginal
Thrombophlebitis during pregnancy (week 27)	0	No	Yes	Prophylactic	No	No	No	Vaginal
Previous pulmonary embolism	0	Yes	Yes	Prophylactic	No	No	Yes	Vaginal
aPL positivity	aCL IgG, B2GP-1 IgG	Yes	Yes	Prophylactic	No	No	Yes[a] attributed to placenta previa	C-section, planned

LMWH, low-molecular-weight heparin; aPL, antiphospholipid antibodies including antibodies against cardiolipin(aCL), B2-glycoprotein-1 (B2GP-1), lupus anticoagulant (LAC); LN, lupus nephritis; LDASA, low-dose acetyl salicylic acid; numbers in parentheses denote previous history of aPL positivity, not confirmed in the index pregnancy; C-section, cesarean section; APS, antiphospholipid syndrome.

[a]Not SLE related.

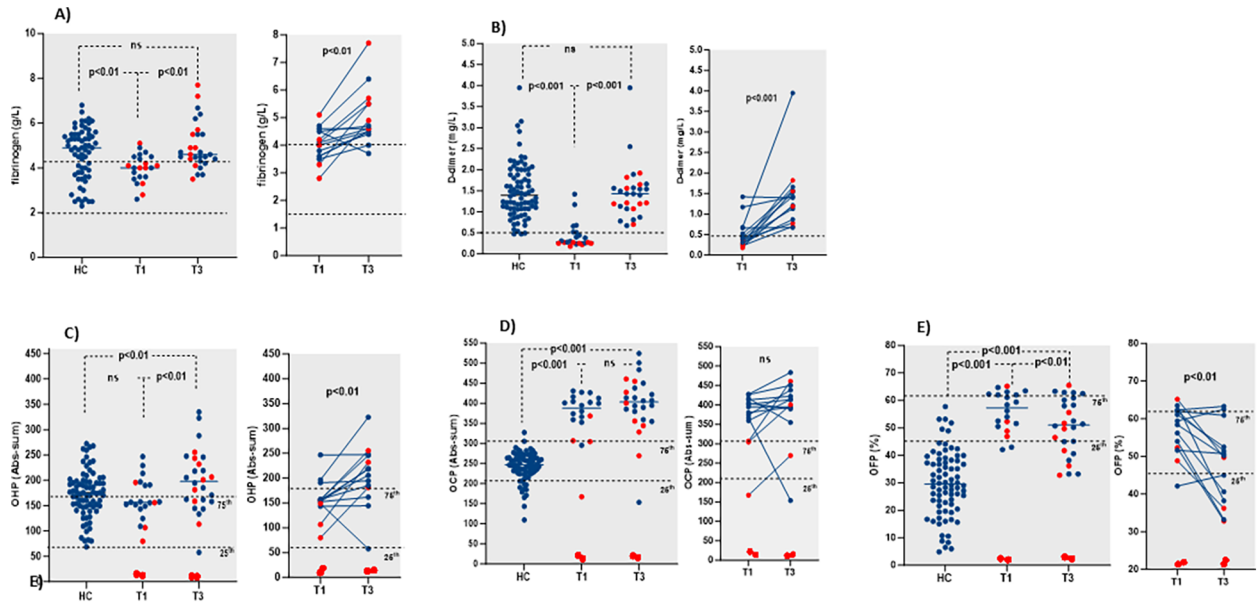

FIGURE 1
Hemostatic parameters (fibrinogen - (A), D-dimer - (B), OHP - (C), OCP - (D) and OFP - (E)) in all patients compared to healthy controls and in relation to LMWH treatment (left). Separate graphs in 16 patients with samples from both T1 and T3 (right). LMWH treated patients marked in red.

D-dimer. Thus, the results of fibrinogen and D-dimer are presented for a total of 28 patients, and the remaining parameters in 26 patients.

Fibrinogen and D-dimer did not differ between the whole group of patients and the controls. OCP was significantly increased in the patients with SLE ($p < 0.001$), while OHP was similar in both groups. OFP was higher in the patients with SLE ($p < 0.001$), however the CLT was not significantly prolonged. When PTCI was added, CLT was significantly shorter in the patient group compared to the control group ($p < 0.001$), thus dCLT was significantly higher ($p < 0.001$). There was a significant inverse correlation between dCLT and OFP in the patient group ($r = -0.60$; $p < 0.01$).

In total, the levels of all the investigated coagulation parameters did not differ between the patients receiving low-dose LMWH prophylaxis and those without Table 3.

There were no differences in the investigated hemostatic variables between the subgroups of patients with a history of LN and those without (data not shown). One patient with active proteinuria received high-dose LMWH prophylaxis and had undetectable levels of parameters investigated by OHP assay.

Pregnancy outcomes and coagulation parameters in patients with preeclampsia

Two patients had early miscarriages and were only studied at T1. Of the remaining 32 patients, four (12.5%) developed PE of whom two had a history of previous LN, one had sAPS, and the fourth had no known predisposition for PE development. Two of the PE patients were primiparous. The two parous patients had a history of gestational hypertension in their previous pregnancies but no further manifestations of PE.

The patient with sAPS was treated with a high prophylactic LMWH dose. One of the LN patients had active proteinuria and was also treated with a high prophylactic dose of LMWH. Two PE patients received LDASA only.

The levels of OCP, OHP, and OFP were undetectable in the patient with sAPS anticoagulated with a high prophylactic LMWH dose. One PE patient receiving a low prophylactic LMWH dose had levels of OCP within the reference range in both T1 and T3, with increasing tendency at T3. In the remaining two patients without LMWH, the OCP levels were above the reference range in both T1 and T3 (Figure 2D).

In T1, OHP was within the reference range in three patients (one with low-dose prophylactic LMWH) and increased above the reference range in T3 (Figure 2C). OFP levels decreased from T1 to T3 as demonstrated in Figure 2E.

There was no difference between the occurrence of LN, APS, or active disease prior to pregnancy when comparing patients with and without PE (data not shown). No thromboembolic episodes occurred during pregnancy.

Analysis of fibrin clot parameters clot structure

The parameters of fibrin clot formation indicated significantly increased Max Abs values and fibrin polymerization rate in the patients with SLE sampled in T3 compared to the HCs (Table 3).

Fibrin clots were analyzed in T1 and T3 in three representative patients with SLE. Scanning electron microscopy (SEM) showed that the fibrin clots in T3 had thinner fibers (mean density 0.28 ± 0.05 µm/fiber) with a denser structure and smaller intrinsic pores compared to the clots created from plasma samples taken during T1 (mean density 0.33 ± 0.02 µm/fiber). The fibrin clot from a patient receiving high-dose prophylactic LMWH during T3 was comprised of thick fibers (mean density 0.63 ± 0.10 µm/fiber) and as such was more prone to fibrinolysis (Figure 3).

TABLE 3 Coagulation parameters in patients with SLE and HCs in the third trimester.

	Pregnant SLE patients (n = 28*)	Pregnant HC (n = 80)	p-value	Pregnant SLE patients without LMWH therapy (n = 18)	Pregnant SLE patients with LMWH therapy (n = 10[a])	$p1$-value
Fibrinogen (g/L)	4.6 (4.3–5.5)	4.9 (3.5–5.5)	NS	4.5 (4.2–5.5)	4.9 (4.3–6.4)	NS
D-dimer (mg/L)	1.4 (1.1–1.6)	1.4 (1.1–1.9)	NS	1.5 (1.0–1.6)	1.2 (1.1–1.7)	NS
OCP (Abs-sum)	403.3 (357.7–444.2)	246.7 (226.7–264.3)	<0.001	406.7 (382.7–444.2)	378.2 (336.5–441.2)	NS
OHP (Abs-sum)	197.7 (158.3–244.7)	175.3 (148.0–197.9)	0.06	189.8 (151.6–246.7)	203.7 (169.7–237.7)	NS
OFP%	51.0 (41.1–60.5)	29.2 (21.0–38.2)	<0.001	52.0 (42.8–61.7)	48.1 (39.0–53.6)	NS
Lag time (s)	220.0 (150.0–300.0)	265.0 (207.0–323.0)	NS	220.0 (150.0–300.0)	252.0 (168.0–304.0)	NS
Max Abs	2.0 (1.8–2.1)	1.36 (1.17–1.55)	<0.01	1.9 (1.7–2.1)	2.0 (1.8–2.2)	NS
Polymerization rate	0.20 (0.16–0.26)	0.47 (0.34–0.60)	<0.001	0.22 (0.19–0.27)	0.17 (0.12–0.21)	NS
CLT (s)	1,630 (1365–1840)	1,533 (1344–1683)	NS	1,570 (1335–1870)	1,725 (1490–1810)	NS
CLT + PTCI (s)	865 (780–960)	1,167 (1032–1275)	<0.001	840 (780–945)	930 (870–1080)	NS
dCLT	790 (550–890)	330 (280–420)	<0.001	740 (550–920)	810 (690–850)	NS

OCP, overall coagulation potential; OHP, overall hemostatic potential; OFP, overall fibrinolysis potential; CLT, clot lysis time; PTCI, potato tuber carboxy-peptidase inhibitor; NS, not significant.

Variables are expressed as median (IQR). P-value presents the differences between patients and controls, $p1$-values present the differences between patients with and without LMWH treatment.

[a]Two patients with SLE had undetectable levels of all hemostatic variables except for D-dimer and fibrinogen due to LMWH treatment. Thus, fibrinogen and D-dimer were presented for 28 patients and the levels of other parameters for 26 patients.

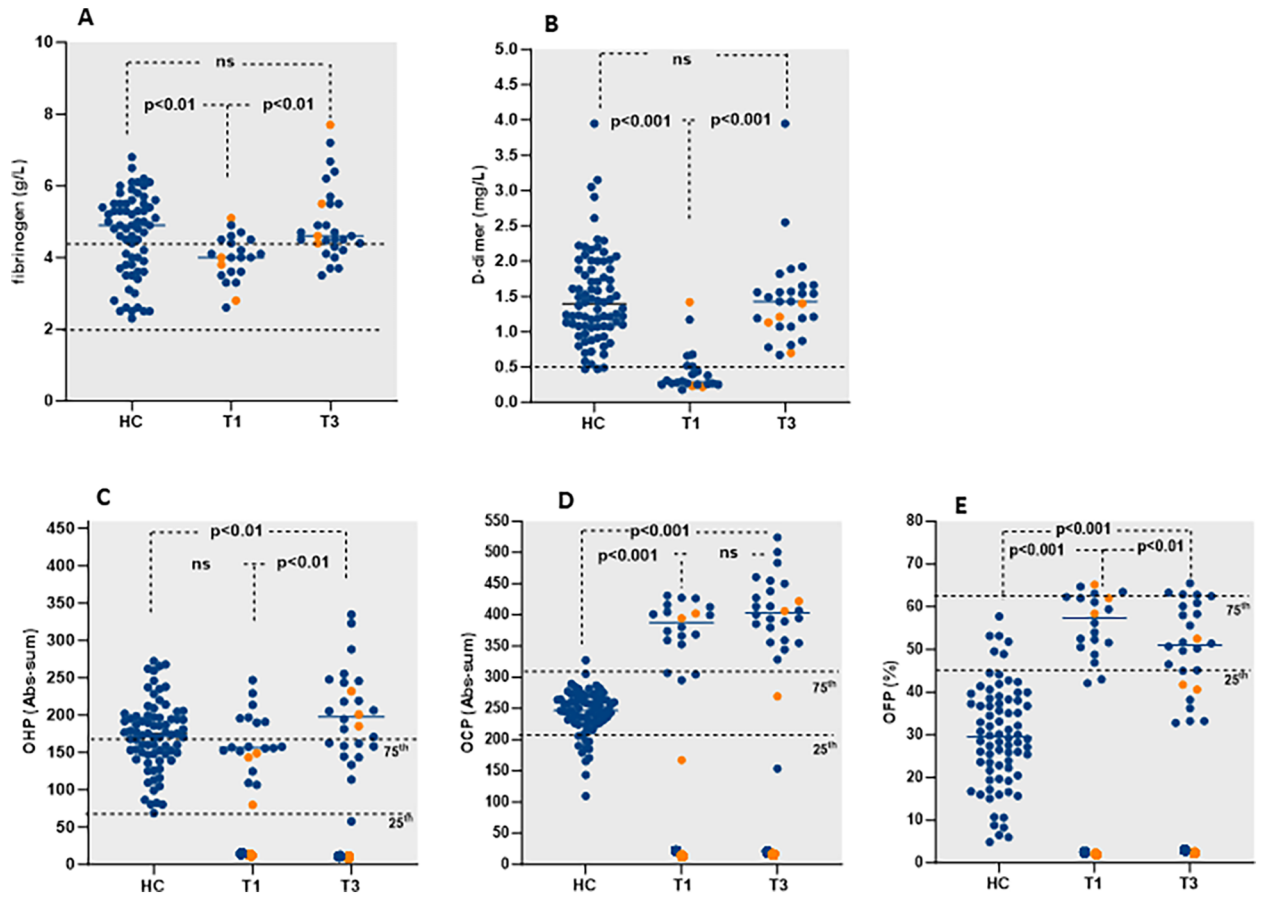

FIGURE 2
Fibrinogen (A), D-dimer (B), OHP (C), OCP (D) and OFP (E) levels in pregnant patients with SLE during first and third trimester of pregnancy and healthy controls. Patients with preeclampsia are marked in orange.

Serology

Anti-dsDNA antibodies were positive in 12/34 (35%) patients in T1 and continued to be persistently positive during the pregnancies (one missing data and one miscarried). None of the patients negative for anti-dsDNA antibodies in T1 had increasing titers during their pregnancy. Positive anti-dsDNA antibodies were found in one of the patients who developed PE.

aPL was positive in seven patients, of whom only one was diagnosed with APS due to a previous arterial thrombotic event. Two patients had a previous history of aPL positivity at low titers but were negative during the current pregnancy. All patients with aPL but one received prophylactic treatment with LMWH: the patient not receiving treatment was the single positive at a low titer for IgG anti-B2GP-I.

Delivery mode and bleeding complications at delivery

Of the 32 patients with full term pregnancies, 23 delivered vaginally (one instrumentally) and 9 by C-section, either planned ($n = 6$) or emergent ($n = 3$). Major bleeding as defined above occurred in 5 of all 32 (15.6%) successful pregnancies. Of these bleeding events, 3/23 (13%) were seen in patients with vaginal delivery, of which two were on LMWH. One patient had received a low prophylactic dose of LMWH and the other patient, with a high prophylactic dose, had a bleeding attributed to uterus atonia. Two out of nine (22.2%) patients with C-sections suffered from major bleeding complications. Of these, one was on LMWH and had a C-section due to placenta previa (Table 2).

Discussion

In this study, we investigated hemostatic parameters in pregnant women with SLE in early and late gestation in association with the use of anticoagulant therapy and the development of PE and thrombotic complications. To the best of our knowledge, this is the first study investigating hemostatic variables during SLE pregnancy. In general, hemostatic alterations toward enhanced coagulation were found in SLE pregnancy compared to healthy pregnant women. In contrast to the parameters of the OHP assay, routine analyses of fibrinogen

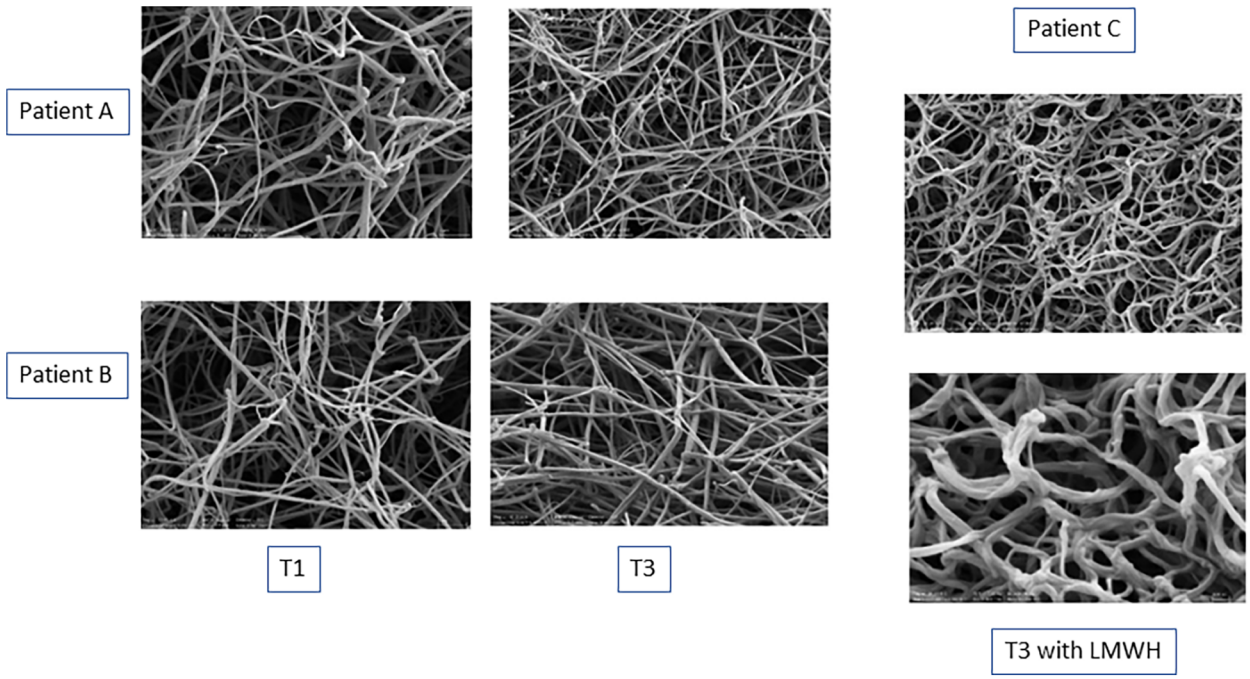

FIGURE 3
SEM images of representative fibrin clots in two pregnant women with SLE during T1 and T3 (patients A and B). A magnification of 1 µm was used for these images. SEM images of a fibrin clot from a patient treated with a prophylactic dose of LMWH during T3 (patient C). A magnification of 1 µm and 200 nm was used for these images.

and D-dimer were not useful for monitoring the effect of LMWH in treated patients.

Pregnancy is recognized as a major risk factor for thromboembolism, with pregnant women being up to six times more likely to develop VTE compared with the general population (25). Thromboembolic complications during pregnancy contribute significantly to maternal morbidity and treatment burden in SLE. A large meta-analysis demonstrated a risk ratio of 11 for the occurrence of thromboembolism during SLE pregnancy as compared to pregnant women without SLE (8). None of the patients included in our study developed thrombotic complications, though enhanced coagulation was found already in early pregnancy and increased over time.

A large proportion of the patients had significantly elevated OCP, OHP, and OFP levels in the third trimester compared to the healthy pregnant women. Yet, the women with SLE had comparably lower OHP during early pregnancy than the healthy controls in the third trimester, pointing toward the importance of sample timing for the interpretation of results. The levels of fibrinogen and D-dimer also increased during pregnancy, yet without differences between the patients with SLE and healthy women in the third trimester of pregnancy. Not unexpectedly, a large individual variation was noted in the markers as we have chosen to display the results of all hemostatic parameters from real-life settings during SLE pregnancies without omitting outliers.

Despite a high prophylactic LMWH dose and LDASA in risk individuals, PE occurred in two cases of which one did not achieve a significant reduction of OCP, OHP, and OFP (for detailed information on the LMWH-treated patients, see Table 2). Overall, the response to the prophylactic LMWH regimen was variable and none of the patients treated with low prophylactic doses achieved a significant anticoagulation measured by the parameters of the OHP assay. The routine coagulation parameters fibrinogen and D-dimer were not affected by LMWH prophylaxis.

The representative fibrin clot images of two patients showed denser clots composed of thinner fibers in T3 compared to T1, revealing the formation of prothrombotic clots during pregnancy in patients with SLE. The increased fibrin polymerization rate indicated faster fibrin formation and Max Abs confirmed higher fibrin density in T3 compared to the healthy controls sampled at the same gestation stage. These clots were more difficult to lyse, however, the CLT did not differ between the healthy pregnant women and SLE pregnancy in our study. This might be due to the increased TAFI activation demonstrated by increased dCLT in the patients with SLE compared to the controls. TAFI (carboxypeptidase B) is an enzyme involved in both coagulation and fibrinolysis (26) and TAFI activation due to enhanced thrombin formation inhibits fibrinolysis, as reflected by the inverse association between dCLT and OFP in the pregnant patients with SLE. However, OFP levels in patients with SLE were elevated compared to the HCs, indicating that other factors may be involved in the overall regulation of the fibrinolytic process during SLE pregnancy, which should be an objective of a larger study.

In one patient treated with a high prophylactic dose of LMWH, SEM images revealed a fibrin clot formed of thicker fibers and

larger intrinsic pores. LMWH and LDASA are known to influence fibrin structure and may lead to increased porosity of fibrin clots and enhanced fibrinolysis (27, 28). However, we could not observe a difference in OFP and CLT between patients treated prophylactically with LMWH and the rest of the patients in our study. Further, despite LDASA, fibrin structure was changed toward a prothrombotic pattern during gestation. This may further support our observation that LDASA and prophylactic LMWH are not sufficient to achieve significant anticoagulation in pregnant patients with SLE.

We found a prevalence of PE of 12.5%, thus a similar frequency as previously reported in pregnant women with SLE (4, 6), although higher frequencies (13%–35%) have also been reported (29). A history of lupus nephritis, chronic hypertension, disease activity before and at conception, and sAPS are known risk factors for PE development in SLE (14). In our cohort, the patient with sAPS with significant anticoagulation developed PE despite full dose LMWH, LDASA, and HCQ treatment. Thus, additional treatment modalities are still warranted to prevent PE development.

No previous PE had occurred in the 14 parous patients. In the two patients who developed PE in their second pregnancy, gestational hypertension was present in the late stages of the previous pregnancies, of whom one also had a previous history of LN. Neither of these two cases had been given LMWH as prophylactic therapy, and LDASA treatment was here not found to be protective for PE development. The use of HCQ, given here to most patients, was in a recent publication not confirmed to decrease the risk for PE development (30).

Prevention of PE and close monitoring of patients at risk are central in the care of pregnant patients with SLE. Furthermore, in a long-term follow-up, women with SLE experiencing hypertensive disorders of pregnancy, including PE, are at increased risk of developing CVD later in life (31). Thus, women with SLE who have developed PE should be closely monitored for hypertension and other CVD risk factors and subjected to vigorous prophylactic treatment to protect them from later vascular events (32, 33).

Major bleeding complications were seen in 5/32 (15.6%) in the total patient population, of which three were treated with LMWH, in all cases given in combination with LDASA. However, other obstetric complications could also have contributed to the hemorrhages and despite anticoagulant treatment, we found no clear signal of increased bleeding risks in our study population. A majority of patients were on LDASA which was not found to increase the rate of severe hemorrhage. However, the numbers are small, and firm conclusions cannot be drawn from the present study.

The major limitation of this study is the small sample size, as larger studies in all trimesters may increase our understanding of the effects of anticoagulation on the risk for bleeding complications, PE development, and prevention of thromboembolism. Our study was performed in a single center, where most of the patients were of Caucasian ethnicity, thus hemostatic alterations may differ between different ethnic groups. In addition, patient data were sourced from clinical records retrospectively, which may have affected data consistency and follow-up compliance. Furthermore, we did not analyze whether the altered hemostatic balance had an impact on fetal outcomes, and no comparison between conventional assays and the OHP/OCP results was performed.

Although all the patients were closely monitored by specialists in obstetrics and rheumatologists in collaboration, compliance to treatment must be considered when evaluating the effects of treatment. The method for the coagulation analysis used in the present study is not routinely available and needs to be automatized to be used in clinical practice to fully monitor the effects of anticoagulant treatment. However, by using this method, we clearly demonstrate that a prothrombotic condition is present among pregnant patients with SLE, which was not captured by conventional assays.

In summary, in this exploratory pilot study aiming at investigating hemostatic alteration in a pregnant SLE population, we found a clear procoagulant state which may have an impact on the risk for the development of PE and thromboembolism. Prophylactic treatment with LMWH was safe regarding bleeding complications but did not ameliorate the hemostatic disturbances. Monitoring of hemostatic alterations may improve personalized treatment strategies in patients at risk.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Swedish Ethical Review Authority and Ethics Committee of Gynaecology and Obstetrics Clinic “Narodni Front”, Belgrade, Serbia. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AA: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing. DL: Formal Analysis, Investigation, Methodology, Writing – review & editing. NS: Formal Analysis, Investigation, Methodology, Writing – review & editing. SL-C: Formal Analysis, Investigation, Methodology, Writing – review & editing. AZ: Writing – review & editing. AM: Writing – review & editing. KB: Conceptualization, Writing – review & editing. MS: Conceptualization, Investigation, Writing – review & editing. FF: Writing – review & editing. ES: Conceptualization, Supervision, Writing – review & editing. LA: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. IG: Conceptualization, Data curation, Formal Analysis, Funding

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Differences in gestational age at preterm birth can predict future cardiovascular events in systemic lupus erythematosus (SLE)

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Introduction: Pregnancy complications from maternal placental syndrome (MPS) are associated with the accelerated development of cardiovascular events (CVE) in the parous cohort with systemic lupus erythematosus (SLE). Preterm birth may result from MPS, which is more common in SLE. This study aimed to determine if preterm birth stratified by gestational age increases the risk of CVE in SLE.

Methods: Utilizing Swedish population databases between 1973 and 2011, those who had been pregnant with SLE were identified and stratified into three groups: term ($\geq 37^{+0}$ weeks), late preterm 34^{+0}–36^{+6} weeks, and early preterm $<34^{+0}$weeks births. The primary outcome was CVE or death from CVE. The risk of CVE was calculated and adjusted for SLE-related morbidity and cardiovascular risk factors.

Results: Over the 38-year interval, there were 3,963 subjects, and the prevalence of preterm birth was 20.9%. The prevalence of CVE was 10.4% ($n = 411$), being highest in those who had given birth $<34^{+0}$ weeks. After multivariable adjustment, the risk of CVE was 1.8 [adjusted hazards ratio (HR) 95% CI: 1.3–2.5] in those who birthed $<34^{+0}$ weeks compared with others who had birthed at term. They also developed CVE earlier than those who birthed at later gestational ages.

Conclusions: Early preterm birth $<34^{+0}$ weeks conferred a two-fold increased hazard for accelerated development of CVE. Reassuringly, those who delivered at a later gestation did not exhibit a similar risk of premature CVE. Therefore, birth $<34^{+0}$ weeks, regardless of an underlying cause, may be a useful screening question to identify parous persons with SLE who are at greater risk of early CVE.

KEYWORDS

systemic lupus erythematosus, pregnancy complication, cardiovascular risk (CV risk), risk stratification, preterm birth, population-based, SLE pregnancy, cardiovascular risk prediction

Introduction

Cardiovascular events (CVE) are more common in young females with systemic lupus erythematosus (SLE), despite having fewer traditional cardiovascular risk factors (1–4). While the etiology is likely multifactorial and linked with antiphospholipid syndrome, studies in the general population have demonstrated associations between adverse pregnancy outcomes especially pre-eclampsia and other complications of placental insufficiency are associated with accelerated cardiovascular events (5, 6). Since those with SLE are also more prone to pregnancy complications, it is likely that preterm birth as a result of these complications could be a marker for CVE.

Our previous work has demonstrated that females with SLE are at greater risk of pregnancy complications; maternal placental syndrome (MPS) is associated with a two-fold increased risk of primary cardiovascular death and CVE (7, 8). MPS is defined as either hypertensive disorders of pregnancy, small for gestational age (SGA), placental abruption, or stillbirth; these features of MPS are also indications for iatrogenic preterm birth to reduce either maternal or fetal morbidity and mortality. Small studies have shown that those with SLE may also have higher rates of spontaneous preterm birth especially if steroids were used at conception (9–11).

Preterm birth is broadly defined as birth before 37 weeks' gestation; many subcategories of preterm birth related to different gestational ages exist in the literature (12). The implications of preterm birth are immense and are closely related to the gestational age at birth; the earlier the gestation at birth, the greater the risk of complications, particularly for the vulnerable premature neonate. Preterm births can occur for a variety of reasons and are not limited to MPS alone. There are different classifications of preterm birth; in the general population, half are spontaneous or idiopathic. Iatrogenic causes and preterm rupture of membranes (PROM) account equally for the remaining 50% (13). In women with SLE, birth may be expedited for maternal and fetal wellbeing to avoid worsening fetal growth restriction (leading to SGA infants), other features of MPS, or active maternal disease.

We aimed to determine the association between different gestational ages of preterm birth and the risk of CVE in a parous cohort with SLE to facilitate future CVE risk stratification.

Methods

Swedish population registries and study design

This was a population-based retrospective cohort study of females with SLE in Sweden between 01/01/1973 and 31/12/2010. Females with SLE were identified using the Swedish National Patient Register (NPR). The personal identity number (PIN) linked NPR data to the Swedish Medical Birth Registry (MBR) and Cause of Death Register. Information on hospital admissions and diagnoses, pregnancies and resulting complications, and cause of death was obtained (14).

Diagnoses were coded using the Swedish International Classification of Disease (ICD) system based on the World Health Organization ICD classification (15). The recording of diagnostic codes is well-validated (15). The Medical Birth Register (MBR) founded in 1973 includes data on 97.0%–99.5% of all pregnancies and births beyond 22 weeks in Sweden (16). The Cause of Death Register contains information on all deaths of Swedish nationals, irrespective of whether the death occurred in Sweden or elsewhere (http://www.socialstyrelsen.se/statistics).

Study cohort and outcomes of interest

Persons with SLE who had a birth and gestational age at birth recorded in the MBR were included. For the survival analysis, those who had a CVE prior to pregnancy were excluded. The outcome of interest was any CVE, including acute coronary syndrome, stroke and peripheral vascular disease, or death from these causes. To explore the severity of preterm birth on the future risk of CVE, length of gestation (or gestational age at birth) was stratified into three categories: (i) $<34^{+0}$ weeks (<239 days) gestation; (ii) 34^{+0}–36^{+6} weeks (239–258 days); and (iii) term $\geq 37^{+0}$ weeks (≥259 days).

MPS was defined as hypertensive disorders of pregnancy, small for gestational age (SGA), placental abruption, or stillbirth. SGA coded independently in the MBR is defined as a birthweight of more than two standard deviations below the mean weight for gestational age, according to the Swedish sex-specific fetal growth curve (17). The other features of MPS were identified through ICD codes.

Statistics

Continuous variables were expressed in medians and interquartile ranges (IQR) and compared using Mann–Whitney *U* or the *t*-test as appropriate. The χ^2 test was used for univariate comparisons of dichotomous data. The risk of CVE was calculated using Cox proportional hazard models and expressed as a hazard ratio (HR). The multivariable analyses included adjustments for age, cardiovascular risk factors (hypertension, renal disease, and diabetes), and SLE-related morbidity (number of inpatient admissions, duration of SLE, cancer, and infections). The cumulative probabilities of survival and time from pregnancy to CVE were estimated using Kaplan–Meier curves and compared using a log-rank test. All *p*-values were two-sided and the threshold for statistical significance was set at $p < 0.05$. Analyses were performed with Stata IC version 13.1 (StataCorp LP, College Station, TX, USA).

Results

Over the 38-year study interval, there were 3,977 females with SLE who had 7,410 pregnancies recorded in the Medical Birth Register, and 3,963 (99.6%) had their length of gestation recorded. At the conclusion of the period of observation, the

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TABLE 1 Characteristics of parous persons with SLE according to their gestational age at birth.

Variables	<34 $^{+0}$ weeks (n = 325)	34 $^{+0}$–36 $^{+6}$ weeks (n = 502)	≥37 $^{+0}$ weeks (n = 3,136)	p-value
Age*, year (IQR)	46 (39–54)	47 (40–55)	51 (42–60)	<0.05$^{\dagger,\ddagger,\$}$
Duration of SLE, years (IQR)	11 (6–20)	10 (5–19)	9 (5–15)	<0.05$^{\dagger,\$}$ ‡0.14
Inpatient admissions, n (IQR)	4 (1–15)	3 (0–10)	2 (0–6)	<0.05,$^{\ddagger,\$}$ †0.07
Hypertension, n (%)	63 (19.4)	74 (14.7)	351 (11.2)	<0.05$^{\dagger,\$}$ ‡0.08
Renal disease, n (%)	84 (25.9)	99 (19.7)	401 (12.8)	<0.05$^{\dagger,\ddagger,\$}$
Diabetes, n (%)	25 (7.7)	36 (7.2)	114 (3.6)	<0.05$^{\ddagger,\$}$ †0.78
Cancer, n (%)	45 (13.9)	50 (10.0)	262 (8.4)	<0.05$^{\$}$ †0.09 ‡0.23
Infection, n (%)	106 (32.6)	145 (28.9)	687 (22.0)	<0.05$^{\ddagger,\$}$ †0.25
Death, n (%)	39 (12.0)	49 (9.8)	236 (7.5)	<0.05$^{\$}$ †0.31 ‡0.08

*Still alive at the conclusion of the study.
†34 $^{+0}$–36 $^{+6}$ vs. <34 weeks.
‡Term (≥37) vs. 34 $^{+0}$–36 $^{+6}$ weeks.
$^{\$}$Term vs. <34 $^{+0}$ weeks.

median age of the cohort who were still alive was 50 (IQR 41–59) years; 324 (8.2%) had died with a median age at death of 52 (IQR 44–59) years. Cardiovascular deaths accounted for 32.4% of all deaths and the median age of CV-related deaths was 54 (IQR 47–60) years. The prevalence of CVE was 10.4% (n = 411), with the median age of first CVE at 51 (IQR 42–57) years. The most common CVE was coronary artery disease accounting for 45.0% of events, with age at first event of 53 (IQR 46–59) years. Stroke was the second most common (38.0%) but occurred at a much younger age [47 (IQR 38–53) years].

Three hundred and twenty-five (8.2%) had a history of any birth <34 $^{+0}$ weeks, 12.7% had birthed between 34 $^{+0}$ and 36 $^{+6}$ weeks, and approximately 80% had only term births of ≥37 $^{+0}$ weeks. Of those who gave birth <34 $^{+0}$ weeks, 63% had MPS complicating their pregnancies. Despite being younger than the other two groups, those who birthed <34 weeks had a longer duration of SLE and increased prevalence of all cardiovascular risk factors and SLE-related morbidity (except for inpatient admissions) compared with those who had term births ($p < 0.05$). Significant differences remained despite a younger age, more renal disease, inpatient admissions, diabetes, and infection between those who gave birth between 34 $^{+0}$ weeks and 36 $^{+6}$ weeks and those who birthed at term (Table 1).

Despite ages being similar across all groups, MPS and all its components were more common in the groups who birthed prior to 37 weeks ($p < 0.05$) (Table 2).

The prevalence of CVE was significantly higher in those who had a previous birth <34 $^{+0}$ weeks' gestation, even when compared with those who gave birth between 34 $^{+0}$ and 36 $^{+6}$ weeks' gestation ($p < 0.05$). CVE occurred much earlier in any parous person who birthed prior to 37 weeks' gestation. More than half of those who birthed <34 $^{+0}$ weeks' gestation died from cardiovascular causes (Table 3).

TABLE 2 Obstetric outcomes and subsequent cardiovascular events in parous persons with SLE according to length of gestation.

Variables	<34 $^{+0}$ weeks (n = 325)	34 $^{+0}$–36 $^{+6}$ weeks (n = 502)	≥37 $^{+0}$ weeks (n = 3,136)
Pregnancies, n	670	1,089	5,624
Time frame of deliveries			
1973–1980	117 (17.5)	218 (20.0)	1,707 (30.4)
1981–1990	202 (30.2)	375 (34.4)	1,615 (28.7)
1991–2000	206 (30.8)	284 (26.1)	1,335 (23.7)
2001–2011	145 (21.6)	212 (19.5)	967 (17.2)
Maternal age at first pregnancy, year (IQR)	26 (23–30)	26 (23–30)	27 (23–30)
Maternal GDM, n (%)	18 (5.5)	29 (5.8)	85 (2.7)
SLE diagnosed prior to pregnancy, n (%)	175 (53.9)	225 (45.0)	864 (27.6)
Livebirth rate, n (%)	615 (91.8)	1,068 (98.1)	5,602 (99.6)
Neonatal survival at 1 month, n (%)	582 (94.6)	1,066 (99.7)	5,596 (99.9)
MPS during any pregnancy, n (%)	205 (63.1)	179 (35.7)	492 (15.7)
Hypertensive disorders, n (%)	100 (30.8)	85 (16.9)	214 (6.8)
Small for gestational age (SGA), n (%)	124 (44.1)	95 (20.1)	274 (8.9)
Stillbirth, n (%)	51 (15.7)	21 (4.2)	22 (0.7)
Placental abruption, n (%)	16 (4.9)	7 (1.4)	18 (0.6)

$p < 0.05$ for all comparisons of obstetric outcomes apart from maternal age and placental abruption when comparing term ≥37 $^{+0}$ weeks vs. 34 $^{+0}$–36 $^{+6}$ weeks.

The subjects contributed 146,754.3 years of person-time to the study. The incidence of CVE in the parous cohort was 27.5 per 10,000 person-years (95% CI: 25.0–30.4). The incidence was higher at 43.7 per 10,000 person-years (95% CI: 33.92–57.5) in

those who had <34 $^{+0}$-week births, and the incidence was 30.2 per 10,000 person-years (95% CI: 2.3–3.9) in those who gave birth between 34 and 36 weeks (Table 3). The risk of developing CVE was 1.8 (95% CI: 1.3–2.4) in those who birthed <34 $^{+0}$ weeks' gestation. The risk of CVE remained elevated in those who had preterm births <34 $^{+0}$ weeks even after adjustment for known CVE risk factors and SLE-related morbidity (Table 3). CVE developed earliest in those with <34 $^{+0}$-week births, compared with those who had term births ($p < 0.001$) (Figure 1).

TABLE 3 CVE in parous persons with SLE stratified by length of gestation.

Cardiovascular event (CVE)	<34 $^{+0}$ weeks (n = 325)	34 $^{+0}$–36 $^{+6}$ weeks (n = 502)	≥37 $^{+0}$ weeks (n = 3,136)
Prevalence of CVE, n (%)	53 (16.3)	56 (11.2)	302 (9.6)
Age at first CVE, year (IQR)	40 (29–47)	47 (38–53)	52 (43–58)
Cardiovascular death, n (%)	21 (53.9)	14 (28.6)	70 (29.7)
Incidence of CVE, per 1,000 (95% CI)	4.4 (3.3–5.8)	3. 0 (2.3–3.9)	2.6 (2.3–2.7)
Unadjusted HR for CVE (95% CI)	1.8 (1.3–2.4)	1.2 (0.9–1.6)	1.0
Adjusted HR 1* for CVE (95% CI)	2.3 (1.7–3.2)	1.5 (1.1–2.0)	1.0
Adjusted HR 2** for CVE (95% CI)	1.8 (1.3–2.5)	1.1 (0.8–1.6)	1.0

*Adjusted HR1—age.
**Adjusted HR2—age, SLE-related morbidity, and cardiovascular risk factors.

Discussion

In this Swedish population of parous persons with SLE, 20.9% had one or more preterm birth <37 $^{+0}$ weeks' gestation. When stratified according to the length of gestation, those with any birth <34 $^{+0}$ weeks had the highest prevalence and incidence of CVE. This study has identified those with SLE who had the greatest need for early cardiovascular screening; this could also provide some reassurance to those who have had a preterm birth at later gestational ages.

Individuals are likely to recollect a preterm birth because of its implications and the need for special care for the neonate and long-term morbidity. Therefore, it serves as an excellent screening question (and is arguably more reliable than a history of pre-eclampsia/hypertensive disorders) for clinicians aiming to identify parous persons with SLE who are at particular risk of CVE.

Globally, preterm births are increasing, due to a variety of reasons (18). Births prior to 37 weeks' gestation in those with SLE may arise as a result of maternal disease and comorbidities, especially MPS-related complications, active SLE during pregnancy, and high doses of corticosteroids which are associated with preterm premature rupture of membranes (19). It is likely that those with severe or active SLE in pregnancy experienced earlier preterm births. Preterm birth unrelated to SLE and its complications can occur spontaneously, but this remains rare, particularly in early preterm births of <34 $^{+0}$ weeks. Only 3.5% of births occurred before 34 weeks in a low-risk American cohort, while the corresponding figure is only 1.8% for Sweden (20). Spontaneous preterm births in those with SLE are usually

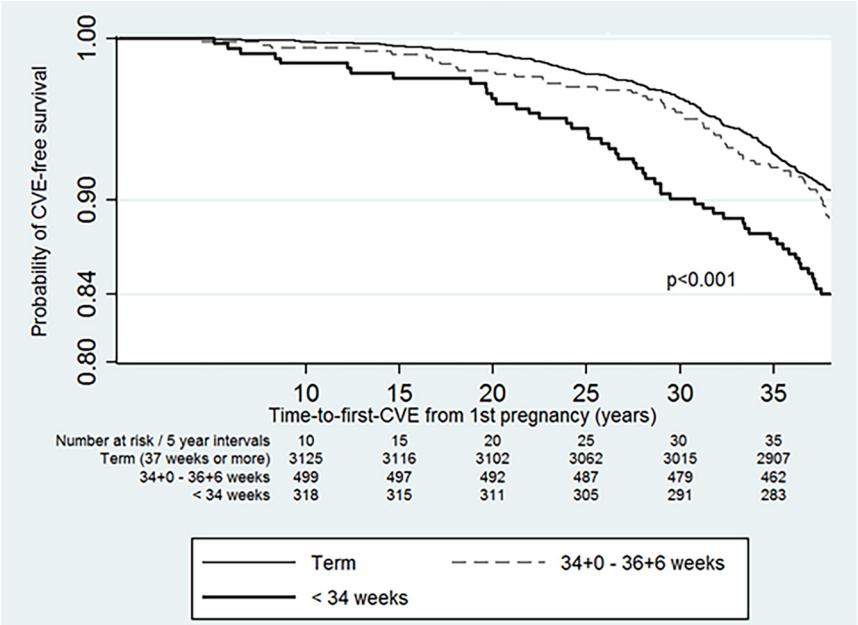

FIGURE 1
Kaplan–Meier survival curves stratified by gestational ages at birth.

the result of preterm rupture of membranes which in turn are associated with steroid use (10, 21). Therefore, it is likely that these spontaneous preterm births are associated with SLE disease activity if not MPS (9, 11). It is not unusual for active SLE in pregnancy to lead to MPS and other adverse obstetric and neonatal outcomes (22). Since there are significant health implications for a neonate delivered prior to 34 weeks, any decision on medically indicated preterm birth would have been taken only after other options to prolong the pregnancy have been exhausted.

This study population is considered at high risk of MPS (22.1% in the Swedish cohort) (7); two-thirds of births prior to 34^{+0} weeks' gestation was associated with MPS-type complications, possibly related to active SLE in pregnancy. Although we were unable to discern the reasons for preterm birth—as SLE activity was not recorded in the MBR—these findings indicate that, regardless of the underlying cause for preterm birth, any birth prior to 34 weeks was associated with an increased risk of accelerated CVE.

It is probable that those with active SLE in pregnancy were more likely to develop MPS and therefore had to be birthed earlier. This is reflected in the greater SLE-related morbidity seen in those who birthed $<37^{+0}$ weeks' gestation.

Registry-based studies are limited to the variables recorded; the present study specifically lacks information about flare or active SLE during pregnancy, the presence of lupus nephritis or other end-organ damage from SLE, steroid and hydroxychloroquine use, and antiphospholipid syndrome, all of which can affect SLE disease activity in pregnancy. The extent of disease damage due to SLE was not available, but we used surrogate markers such as hospital admissions, infections, and development of malignancies and adjusted for these factors in our multivariate analysis. There are multiple shared risk factors between cancer and cardiovascular disease, e.g., obesity, smoking, and social determinants of health, demonstrating how these two conditions are fundamentally interconnected (23). Furthermore, malignancy in SLE is associated with a higher risk of disease damage and immunosuppression (23, 24). Information on other traditional cardiovascular risk factors such as dyslipidemia, family history of premature coronary artery disease, smoking, and obesity were not available; we adjusted for those that were present including hypertension, presence of diabetes, and renal disease. However, as previously summarized in our publications, large international cohorts of SLE patients have not consistently demonstrated that these are useful markers for predicting CVE in patients with SLE, particularly young females (1, 4).

On the other hand, our data from Swedish population registries were drawn from one of the most comprehensive long-term population-based studies, followed up longitudinally over a 38-year interval. Sweden's population registries are a world-renowned example of meticulous record keeping. These data are particularly robust as the length of each gestation is recorded in the MBR and is not subject to recall bias. In addition, Sweden has the highest recorded prevalence of SLE in the Nordic countries where thorough records exist, although this may partly be due to ascertainment bias because of very reliable national records (25).

In conclusion, preterm birth <34 weeks' gestation could be a useful screening question for clinicians identifying parous individuals with SLE at risk of CVE, as they have a two-fold increased likelihood of premature CVE.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Regional Board of Ethics in Stockholm PROTOKOLL 2012/3:2. The studies were conducted in accordance with local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

MS: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. CN-P: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. MW: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. LM: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. DP: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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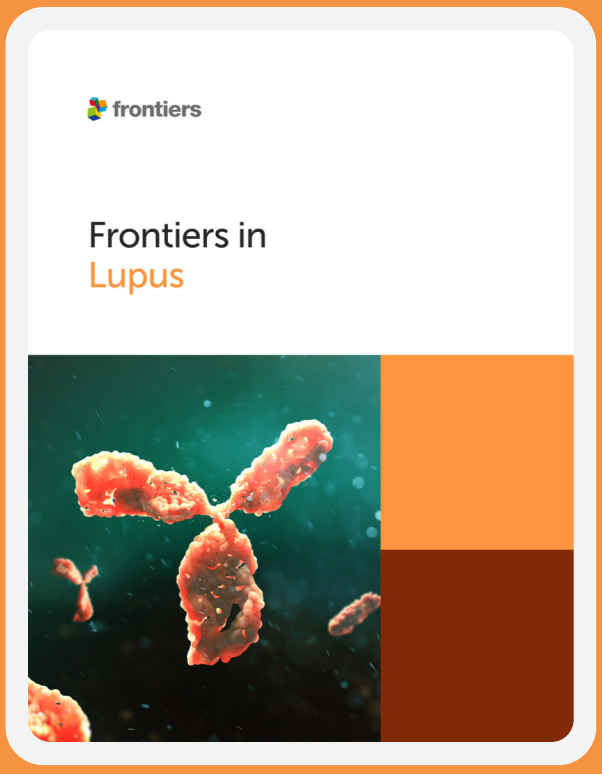

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