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Impact of pregnancy in patients with systemic lupus erythematosus-associated pulmonary arterial hypertension: case series and literature review

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ABSTRACT

Objective This study aimed to investigate the clinical characteristics and outcomes of pregnancy complicated by SLE-associated pulmonary arterial hypertension (SLE-PAH) in a case series and literature review.

Methods This single-centre retrospective study included 10 consecutive pregnancies complicated by SLE-PAH confirmed by right heart catheterisation (RHC) at Peking Union Medical College Hospital between 2009 and 2020. A literature search was conducted and 14 pregnancy cases complicated by SLE-PAH were reviewed.

Results At the time of 10 patients' initial visits, the average age was 30.00±5.72 years and the median disease duration of SLE and PAH was 34.5 (range 1–164) months and 2 (1–51) months. Two patients carried planned pregnancy, seven patients developed PAH during pregnancy and one pregnancy was unplanned. Further, nine patients had low disease activity, with Systemic Lupus Erythematosus Disease Activity Index between 0 and 4, and 30%, 30% and 40% of patients were of WHO functional class II, III and IV, respectively. All patients were evaluated by RHC and echocardiography. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were elevated in 70% of patients, with a median level of 776 (56–18 023) pg/mL. The median time of completed pregnancies in all patients was 31 (15–38) weeks and six patients delivered live infants. SLE activity and PAH severity improved in 70% of patients within 6 months after delivery. One patient died on the 15th day after induction of labour. In the remaining patients, all achieved a lupus low disease activity state; according to the European Society of Cardiology/European Respiratory Society risk stratification, seven were categorised at a lower risk state compared with their risk stratification during pregnancy, and two remained at intermediate risk. Additionally, 80% of patients exhibited mild impairments with WHO functional class I or II. The median NT-proBNP level was 184 (32–4003) pg/mL within 6 months after delivery. In the reviewed literature, the average age of patients was 30.09±5.37 years. The median time of completed pregnancies was 36 (28–40) weeks. More cases were planned and successful, and the survival rates of mothers and neonates were 85.71% and 92.86%, respectively.

Conclusions Successful pregnancy could be possible in women with SLE-PAH if SLE-PAH treatment goals are achieved under proper therapies, careful monitoring and thorough evaluations.

Key messages

What is already known about this subject?

- Pregnancy is a serious condition in women of childbearing age with SLE-associated pulmonary arterial hypertension (SLE-PAH).
- Several successful pregnancies have been reported in patients with SLE-PAH; however, there is a lack of publications and guidelines on decision-making and management of pregnancy in SLE-PAH.

What does this study add?

- This study included 10 consecutive pregnant patients with SLE-PAH confirmed by right heart catheterisation and reviewed 14 cases from previous studies.
- The overall survival rates of mothers and neonates were 87.5% and 79.17%, respectively.
- Successful pregnancy may be possible in reproductive-age women with SLE-PAH when SLE-PAH is well controlled and treatment goals are achieved through careful planning and appropriate PAH-specific therapies.

How might this impact on clinical practice or future developments?

- Pregnancy in this population is still a major challenge for both patients and physicians; however, a combination of proper therapy, monitoring and evaluation may contribute to lowering the risk of adverse events in pregnancy cases complicated by SLE-PAH.

INTRODUCTION

SLE is a multisystem autoimmune disease that mainly occurs in women of childbearing age. Advances in therapy and management over the past several decades have facilitated satisfaction of fertility needs of most women with SLE.[1] Pulmonary arterial hypertension (PAH) is a rare but severe complication of SLE, with incidence varying from 2.06% to 3.83% in affected patients.[2–4] Due to rapid

disease progression and lack of effective treatments, the prognosis for patients with SLE-PAH is worse than for those with SLE alone, with a 3-year survival rate of 45.0%–89.4%.[5–8]

Pregnancy in patients with SLE-PAH is recognised as a serious and complicated scenario as it can result in negative consequences for both mothers and neonates, especially maternal death.[9–12] Additionally, few publications and guidelines have focused on decision-making and management of pregnancy in women with SLE-PAH. Several recent case reports have shown that pregnancy is feasible in patients with SLE-PAH.[13–20] These investigations suggested the possibility of successful pregnancy complicated by SLE-PAH and served as the foundation for future management and treatment guidelines.

This is the first study of pregnant women with SLE-PAH confirmed by right heart catheterisation (RHC) and the first systematic review of all eligible pregnancy cases complicated by SLE-PAH reported in previous studies. Our study provides an overview of the clinical characteristics, management and outcomes of pregnant women with SLE-PAH.

METHODS

Subjects

This single-centre retrospective study was conducted at Peking Union Medical College Hospital. Consecutive pregnancy cases complicated by SLE-PAH were collected from May 2009 to September 2020. A search for inpatient and outpatient data in the hospital information system of Peking Union Medical College Hospital and the Chinese Lupus Treatment and Research Group registry was performed. All applicable medical records for patients were reviewed. Cases were included if (1) the patient fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria for SLE; (2) the patient had a diagnosis of PAH with mean pulmonary artery pressure (mPAP) ≥25 mm Hg confirmed by RHC; and (3) PAH was diagnosed before or during pregnancy. A completed pregnancy included pregnancy with induced labour or uninduced labour (including liveborn infants by vaginal or caesarean and stillbirth). Planned pregnancy was defined as planning of the pregnancy by the patient with awareness of potential risks in coordination with family members and physicians. Extracted patient demographics included age, disease duration, whether the pregnancy was planned and autoantibody levels. Obstetric characteristics were collected including pregnancy history, time of pregnancies completed, mode of delivery and anaesthesia, and maternal and neonatal outcomes. Clinical evaluation of SLE was based on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), organ involvement, the American College of Rheumatology/SLICC Damage Index and Physician Global Assessment. Assessment of PAH was according to the European Society of Cardiology/European Respiratory Society (ECS/ERS) risk stratification, including related symptoms and their progression, WHO functional class, echocardiography results, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels at baseline and within 6 months after delivery.[21–23]

Literature review of pregnancy cases complicated by SLE-PAH

We conducted a literature search in PubMed before 7 August 2021, with combined terms of PAH and pregnancy (online supplemental figure 1). Studies were eligible if (1) the patient was diagnosed with SLE using a validated standard diagnosis; (2) the patient had a diagnosis of PAH confirmed by either RHC or echocardiography (mPAP ≥25 mm Hg); (3) PAH was diagnosed before or during pregnancy; (4) the study was an original study published in English, including a case report, case series, case–control or retrospective cohort study; and (5) detailed medical information could be obtained. The exclusion criteria were as follows: (1) pulmonary hypertension was due to other causes, such as idiopathic PAH, heritable PAH, and pulmonary hypertension secondary to cardiac and interstitial lung diseases; and (2) there is a lack of detailed clinical records of the patient, including WHO functional class or mPAP level, and maternal outcomes. Eleven studies were finally included in the literature review, seven of which were case reports and four were retrospective studies; relevant medical information was then extracted.

Statistical methods

Descriptive and continuous data are shown in the tables. Descriptive data were presented as percentages. Continuous data were expressed as mean±SD or median (range) if they do not conform to a normal distribution. Data were analysed using SPSS V.23.0 and Prism V.9 (GraphPad Software, La Jolla, California, USA).

RESULTS

Baseline characteristics

Ten pregnant women who were diagnosed with SLE-PAH between April 2012 and August 2019 were identified at our hospital. Patient baseline characteristics and disease evaluation results are shown in table 1. The average age at the patients' first visits during pregnancy was 30.0±5.7 years. The median disease duration of SLE and PAH at baseline was 34.5 (range 1–164) months and 2 (1–51) months, respectively. Among these 10 patients, 2 planned their pregnancy with a full understanding of the risks and possible harm, 7 patients developed PAH during their pregnancy, and 1 pregnancy was unplanned (case 5). Nine cases were multigravida, and five primiparas were enrolled in this study. None of these women experienced previous pregnancy-related complications, such as pre-eclampsia or intrauterine growth restriction. Detailed pregnancy histories are reported in table 1.

All cases were positive for ANA, seven were positive for anti-Sjogren's syndrome antigen A (anti-SSA), two were positive for anti-Sjogren's syndrome antigen B (anti-SSB) and two were positive for anti-double strand DNA

Table 1 Baseline clinical characteristics of 10 pregnant patients with SLE-PAH and assessment of SLE and cardiac function

	Baseline clinical characteristics					Baseline assessment of SLE							Baseline assessment of cardiac function										
							Autoantibody							Right heart catheterisation				Echocardiography					NT-proBNP (pg/mL)
Case number (year of pregnancy)	Age	SLE duration (months)	PAH duration (months)	Planned pregnancy under awareness of risk*	Pregnancy history	SLE-associated manifestations	ANA	Anti-SSA	Anti-SSB	Anti-dsDNA	aPLs	SLEDAI	WHO functional class	mPAP (mm Hg)	PAWP (mm Hg)	CO (L/min)	PVR (WU)	PASP (mm Hg)	RVTD (mm)	EF (%)	TAPSE (mm)	Pericardial effusion	
1 (2012)	22	17	3	16 weeks	G2P0A1L0 (spontaneous abortion)	▶ Constitutional. ▶ Haematological. ▶ Mucocutaneous. ▶ Serosal. ▶ Musculoskeletal.	+	+	–	–	–	14	IV	33	6	5.3	5.09	98	NR	NR	NR	NR	9098
2 (2015)	35	1	1	12 weeks	G2P1A0L1	▶ Constitutional. ▶ Mucocutaneous. ▶ Serosal. ▶ Musculoskeletal.	+	+	–	–	–	2	III	25	5	5.8	3.45	55	45	69	NR	Moderate	125
3 (2019)	35	52	51	Yes	G3P1A1L1 (spontaneous abortion)	▶ Musculoskeletal.	+	+	–	–	NR	4	II	41	7	6.5	5.23	99	40	75	17	No	56
4 (2016)	29	92	4	31 weeks	G5P1A3L1 (all spontaneous abortions)	▶ Haematological. ▶ Mucocutaneous. ▶ Serosal. ▶ Musculoskeletal.	+	–	–	–	–	2	IV	66	11	4.4	12.50	93	45	55	11	Trace	4497
5 (2018)	29	66	9	No	G1P0A0L0	▶ Mucocutaneous. ▶ Musculoskeletal.	+	–	–	+	–	2	II	28	8	6.5	3.08	39	NR	62	23	No	293
6 (2018)	19	8	1	20 weeks	G4P0A3L0 (all elective abortions)	▶ Haematological.	+	–	–	–	–	2	IV	47	16	1	31.00	102	42	71	10	Trace	18 023
7 (2019)	34	1	1	22 weeks	G2P0A1L0 (induced labour)	▶ Serosal.	+	+	+	–	–	0	II	31	NA	5	NA	71	34	69	18	Trace	142
8 (2019)	36	2	1	29 weeks	G4P1A2L1 (all elective abortions)	▶ Constitutional. ▶ Haematological. ▶ Renal.	+	+	–	–	–	3	IV	NA	NA	NA	NA	41	35	55	NR	No	1963
9 (2016)	29	104	41	Yes	G2P0A1L0 (spontaneous abortions)	▶ Mucocutaneous. ▶ Musculoskeletal.	+	+	+	+	–	2	III	44	8	5.9	6.10	78	44	70	15	No	89
10 (2018)	32	164	1	36 weeks	G2P1A0L1	▶ Mucocutaneous. ▶ Serosal.	+	+	–	–	–	0	III	35	2	5.2	6.35	72	41	74	16	No	1259

Pregnancy history: G, gravida; P, para; A, abortus; L, living.
SLE-associated manifestations (domain): constitutional (fever), haematological (leucopenia, thrombocytopaenia, autoimmune haemolysis), neuropsychiatric (delirium, psychosis, seizure), mucocutaneous (alopecia, oral ulcers, subacute cutaneous lupus erythematosus/discoid lupus erythematosus, acute cutaneous lupus erythematosus), serosal (effusion, acute pericarditis), musculoskeletal (joint involvement) and renal (proteinuria, class II/V lupus nephritis, class III/IV nephritis).
Autoantibody: +, positive; –, negative.
aPLs include anticardiolipin, anti-beta(2)-glycoprotein I and lupus anticoagulant.
Some data for case 7 and case 8 were not available due to data missing.
*In patients developing PAH during pregnancy, gestational week of PAH diagnosis is reported.
anti-dsDNA, anti-double strand DNA; anti-SSA, anti-Sjogren's syndrome antigen A; anti-SSB, anti-Sjogren's syndrome antigen B; aPLs, antiphospholipid antibodies; CO, cardiac output; EF, ejection fraction; mPAP, mean pulmonary artery pressure; NA, not available; NR, not reported; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RVTD, right ventricular transverse diameter; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; TAPSE, tricuspid annular plane systolic excursion; WU, Woods unit.

(anti-dsDNA). Nine patients with reported laboratory results were all negative for antiphospholipid antibodies, including anticardiolipin, anti-beta(2)-glycoprotein I and lupus anticoagulant. Nine patients had low disease activity, with SLEDAI between 0 and 4. The SLEDAI score of case 1 was 14, indicating moderately active SLE.

Right heart function was assessed using clinical features and laboratory data. The percentages of patients with WHO functional class I, II, III and IV were 0%, 30%, 30% and 40%, respectively. RHC is the gold standard for the diagnosis of PAH and was used to evaluate PAH at all of the patients' first visits. As listed in table 1, all patients had an elevated mPAP (≥25 mm Hg) and pulmonary vascular resistance (PVR ≥3 Woods unit, WU). The median mPAP, pulmonary artery wedge pressure, cardiac output and PVR were 35 (25–66) mm Hg, 7.5 (2–16) mm Hg, 5.3 (1–6.5) L/min and 5.67 (3.08–31.00) WU, respectively. Echocardiography was used to evaluate PAH and monitor patients' cardiac function during pregnancy as it is a non-invasive measurement. The median pulmonary arterial systolic pressure (PASP) was 75 (39–102) mm Hg. The median tricuspid annular plane systolic excursion (TAPSE) was 16 (10–23) mm, indicating impaired right ventricular function in most patients. However, dilation of right ventricle was not observed in any of the patients and no reduction in ejection fraction (EF) was found in nine patients with recorded EF. Only one patient (case 2) was confirmed to have a moderate pericardial effusion via echocardiography. NT-proBNP levels were elevated in 70% of patients, with a median of 776 (56–18 023) pg/mL in all cases. Detailed baseline characteristics are presented in table 1.

Maternal and neonatal outcomes

Nine of 10 patients were administered corticosteroid therapy during pregnancy. Immunosuppressive agents, PAH-targeted medications and supportive treatments were adjusted according to patients' manifestations and drug teratogenicity around pregnancy (online supplemental table 1).

Four out of 10 patients underwent induced labour. Among the other six pregnancies without induced labour (including both planned pregnancies, cases 3 and 9), five patients delivered their neonates via caesarean section and one delivered vaginally. The median time of pregnancies completed in all patients, patients with induced labour and patients without induced labour was 31 (15–38) weeks, 22 (15–25) weeks and 33 (31–38) weeks, respectively. Of the 10 patients, 40% were administered general anaesthesia and 60% were administered continuous epidural anaesthesia.

Table 2 shows that most patients in our study benefited from completed pregnancies regardless of its form. In general, SLE activity and PAH severity improved in 70% of patients and remained stable in 20% of patients within 6 months after delivery. One patient (case 6) died of shock caused by deterioration of cardiac function and infection 15 days after induced labour. In the other patients, SLEDAI remained 0–4, no disease flared and no new organ was involved within 6 months after delivery, indicating a lupus low disease activity state. According to ECS/ERS risk stratification, all alive patients were categorised at a lower risk state compared with their risk stratification during pregnancy, except for cases 3 and 5 who remained at intermediate risk. Regarding cardiac function evaluated using WHO functional class within 6 months after delivery, 80% of patients exhibited mild impairments (WHO functional class I or II). The median PASP of all surviving patients was 59 (23–83) mm Hg, indicating the improvement of PAH in this group. The median TAPSE was 15 (14–21) mm, which was similar to the level at baseline. Pericardial effusion could not be detected after delivery in case 2. In all surviving patients, the median of NT-proBNP level decreased from 293 (56–9098) pg/mL at baseline to 184 (32–4003) pg/mL within 6 months after delivery. Decreases in NT-proBNP levels were especially remarkable in patients with NT-proBNP levels higher than 10-fold upper limit of normal (ULN, 125 pg/mL) at baseline. It was also observed that the levels of NT-proBNP were lower than threefold ULN in eight out of nine surviving patients (figure 1A). However, several results of echocardiography indicated deterioration of cardiac function within 6 months after delivery. Right ventricular dilation was not detected in most patients, except for case 4, whose right ventricular transverse diameter was 50 mm. It was notable that reduction in EF was found in two out of eight patients with recorded EF.

Despite prematurity and low birth weight in most of six neonates, the 5 min Apgar scores of all infants were in the normal range (7–10). Five of six infants were admitted to the neonatal intensive care unit for 4–30 days due to preterm birth and/or low birth weight. There was no neonatal mortality, and no severe diseases were reported in these children until the last follow-up in January 2022.

Literature review

A review of the literature included 14 pregnancy cases complicated by SLE-PAH in 11 studies from 2002 to 2021.[13–18 24–28] Most patients (except for the case in Zhou *et al*[24]) delivered via caesarean section (76.92%); the others delivered vaginally (23.08%). The low proportion of induced labour was the most distinct characteristic of the cases in the literature compared with cases at our hospital. However, these patients shared some similar clinical features with the patients at our hospital. The average age of patients from our literature review was 30.09±5.37 years. The median time of their completed pregnancies was 36 (28–40) weeks, which was similar to the data for patients with uninduced labour at our hospital. Further, more pregnancies were planned in the 14 reviewed cases. Regarding obstetric outcomes, the survival rates of mothers and neonates were 85.71% and 92.86% respectively. Assessment of cardiac function at baseline and/or after delivery, including WHO functional class and levels of mPAP and NT-proBNP, was reported in some of the cases from the reviewed literature. WHO functional class

Table 2 Maternal and neonatal clinical outcomes and assessment of cardiac function of 10 pregnant patients with SLE-PAH within 6 months after delivery

	Maternal clinical outcomes				Neonatal clinical outcomes					Assessment of cardiac function						
											Echocardiography					
Case number	Week of completed pregnancies (gestational age, weeks)	Mode of delivery	Anaesthesia	Maternal status (compared with baseline)	Neonatal status	Birth weight (g)	5 min Apgar score	NICU stay duration (days)	Severe diseases	WHO functional class	PASP (mm Hg)	RVTD (mm)	EF (%)	TAPSE (mm)	Pericardial effusion	NT-proBNP (pg/mL)
1	24+0	Induced labour	Epidural	Improved			NA			II	56	NR	NR	NR	NR	32
2	15+6	Induced labour	General	Improved			NA			II	34	34	63	21	No	170
3	35+4	Caesarean	Epidural	Stable	Alive	2820	10	5	No	I	86	41	67	15	No	127
4	31+0	Vaginal	Epidural	Improved	Alive	1700	10	10	No	IV	83	50	71	15	Trace	4003
5	38+2	Caesarean	Epidural	Stable	Alive	3000	10	0	No	II	49	44	35	NR	No	238
6	20+4	Induced labour	General	Death			NA			IV	NA	NA	NA	NA	NA	26 988
7	25+5	Induced labour	General	Improved			NA			II	59	32	71	20	No	66
8	31+5	Caesarean	Epidural	Improved	Alive	1500	10	20	No	II	23	NR	48	NR	No	186
9	31+2	Caesarean	Epidural	Improved	Alive	1400	8	30	No	II	84	39	78	14	No	184
10	36+5	Caesarean	General	Improved	Alive	<2500 (no exact data)	10	4	No	II	78	44	68	15	No	316

Echocardiography: PASP (pulmonary arterial systolic pressure).
EF, ejection fraction; NA, not applicable; NICU, neonatal intensive care unit; NR, not reported; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; RVTD, right ventricular transverse diameter; SLE, systemic lupus erythematosus; TAPSE, tricuspid annular plane systolic excursion.

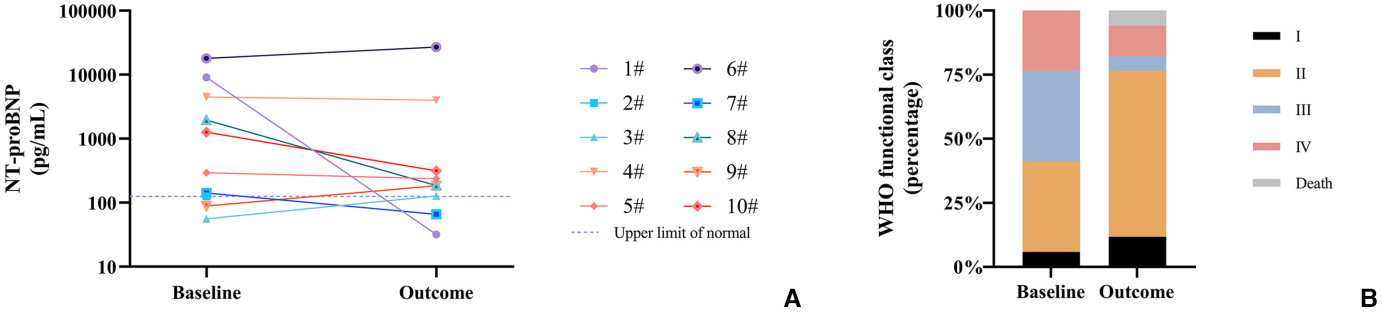

Figure 1 NT-proBNP and WHO functional class of pregnant patients with SLE-PAH at our hospital and previous studies at baseline and within 6 months after delivery. (A) NT-proBNP of 10 pregnant patients with SLE-PAH at our hospital at baseline and within 6 months after delivery. (B) WHO functional class of 17 pregnant patients with SLE-PAH at our hospital and previous studies at baseline and within 6 months after delivery. NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension.

at baseline and after delivery was available in seven cases in the literature and ten cases at our hospital. Figure 1B illustrates that in these 17 patients, the percentage of patients with WHO functional class I and II rose from 41.18% to 76.47%. Further clinical characteristics, outcomes and assessment of cardiac function are displayed in table 3.

DISCUSSION

This is the first retrospective study of consecutive pregnancy cases complicated by SLE-PAH confirmed by RHC. In our case series and literature review, we explored the possibility of pregnancy in patients with SLE-PAH by comprehensively analysing obstetric outcomes and critically evaluating primary disease and cardiac function.

The mortality of pregnant patients with PAH ranges from 12% to 56%,[29 30] which is much higher than that of healthy population. Previous evidence has suggested that connective tissue disease-associated PAH may be related to lower survival rates and worse prognosis compared with other types of PAH.[31] A majority of pregnant women with other types of PAH had better cardiac function than our patients.[30] Therefore, more attention and more intensive interventions are needed in PAH secondary to connective tissue diseases. Recently, outcomes of patients with connective tissue disease-associated PAH have significantly improved with advances in treatment-to-target therapies and novel target drugs. Some prior studies have even reported successful pregnancies in women with SLE-PAH, similar to the cases in our study. The improved survival can be attributed to proper management based on treatment-to-target therapy during the entire pregnancy. Our study demonstrated that maternal death did not occur in planned cases; however, it happened in two of ten unplanned cases, suggesting that planning prior to pregnancy may be associated with improved maternal survival. Moreover, in all successful delivered cases at our hospital, patients had SLEDAI scores ranging from 0 to 4 at baseline. Therefore, low disease activity may contribute to successful pregnancies in patients with SLE-PAH. Advanced and thorough evaluation by rheumatologists, PAH specialists, obstetricians, intensive care specialists and obstetric anaesthetists is suggested to minimise disease activity and organ damage and to optimise health-related quality-of-life in pregnant women with SLE-PAH.[32] Taken together, a comprehensive management can considerably decrease the risks of pregnancy and improve prognoses in patients with SLE-PAH. It is recommended that shared decision on pregnancy should be made between informed patients, her family members and her physicians.

Most studies of pregnant women with pulmonary hypertension have only focused on congenital heart disease-associated pulmonary hypertension, which has exhibited good response to target therapy and tends to improve significantly through treatment. Unlike congenital heart disease-associated pulmonary hypertension, SLE-PAH is considered a potentially reversible condition because its severity is positively correlated with level of inflammation[33–36] and disease activity of SLE.[37] Therefore, earlier and intensive immunosuppressive treatment for SLE is one of the most important components of a successful pregnancy outcome in a patient with SLE-PAH.

PAH-specific treatment is another important pillar of a treatment-to-target therapy in pregnant patients with SLE-PAH. Advances in target therapies have allowed successful pregnancies in patients with congenital heart disease-associated PAH.[10 38 39] Target therapies have also been used in pregnant patients with SLE-PAH in several case reports.[13 25 27] A combination therapy may further improve exercise tolerance, quality of life and patient survival.[40–42] Phosphodiesterase-5 inhibitors and prostacyclin receptor agonists are relatively safe with the Food and Drug Administration (FDA) pregnancy category B (tadalafil, vardenafil, treprostinil) and C (iloprost), and can be used when necessary during pregnancy complicated by SLE-PAH. However, special attention must be paid to certain endothelin receptor antagonists and guanylate cyclase agonists (such as riociguat), which have teratogenic effects and must be avoided during pregnancy.[43 44] Additionally, the comprehensive application of inotropic, diuretics, anti-infection, antiplatelets and anticoagulants, and oxygen therapies also has a positive effect on haemodynamic parameters and maternal outcomes.[45 46]

Table 3 Literature review of cases of pregnancy in patients with SLE-PAH

	Clinical characteristics and outcomes							Assessment of cardiac function		
Article	Age	Planned pregnancy under awareness of risk	Week of completed pregnancies (gestational age, weeks)	Mode of delivery	Anaesthesia	Maternal outcomes (cause of death, if applicable)	Neonatal status	WHO functional class (baseline, outcome, if outcome available)	mPAP (mm Hg) (baseline, outcome, if outcome available)	Baseline NT-proBNP (pg/mL)
Zhou *et al*[24]	19	No	NR	NR	NR	Death (heart failure, PAH crisis)	Death	IV	NR (RHC confirmed)	NR
Lim *et al*[25]	33	No	40+6	Vaginal	Epidural	Alive	Alive	(II, II)	42.8	1241
	38	No	36+4	Vaginal	Epidural	Alive	Alive	(II, II)	34.1	79
Meng *et al*[26]	NR	No	34	Vaginal	Epidural	Alive	Alive	II	NR (25–50)	NR
	NR	Yes	29	Caesarean	Spinal	Alive	Alive	IV	NR (≥50)	NR
	NR	Yes	32	Caesarean	Epidural	Alive	Alive	IV	NR (≥50)	NR
Corbach *et al*[27]	28	No	37+1	Caesarean	Spinal	Alive	Alive	(III, III)	NR (RHC confirmed)	70
Goland *et al*[13]	30	No	36+3	Caesarean	NR	Alive	Alive	(II, II)	51.7	NR
McMillan *et al*[28]	30	No	31	Caesarean	General	Death (acute postpartum cor pulmonale, small vessel lung disease)	Alive	NR	70–80	NR
Tabarsi *et al*[14]	39	No	36	Caesarean	Epidural	Alive	Alive	(III, II)	NR (PASP 83)	NR
Streit *et al*[15]	29	Yes	37	Caesarean	Epidural	Alive	Alive	(III, IV)	(35, 21)	70
Kawabe *et al*[16]	31	Yes	28+1	Caesarean	General	Alive	Alive	(I, I)	(34, 34)	NR
Mirdamadi *et al*[17]	30	No	36	Caesarean	General	Alive	Alive	NR	(47, 110)	NR
Smith *et al*[18]	24	Yes	28+1	Caesarean	General	Alive	Alive	NR	49	NR

mPAP, mean pulmonary artery pressure; NR, not reported; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; RHC, right heart catheterisation; SLE, systemic lupus erythematosus.

This case series is limited by its small size and broad time range of pregnancy cases complicated by SLE-PAH. Moreover, most of the reviewed literature set out to introduce successful managements of SLE-PAH pregnancy. Therefore, potential bias, such as an overestimation of the survival rate, in prior studies needs to be considered.

CONCLUSION

In conclusion, the results of this case series and literature review confirm that pregnancy is still a significant challenge for both patients and physicians; however, through careful planning and appropriate PAH-specific therapies, a successful pregnancy could be possible in women of reproductive age with SLE-PAH, especially when SLE-PAH is controlled quite well and treatment goals are achieved. Collaboration between patients, family members and physicians contributed to achieving a successful pregnancy outcome with awareness of potential risks. Therefore, a combination of proper therapy, monitoring and evaluation may contribute to lowering the risk of adverse events in pregnancy cases complicated by SLE-PAH. More attention should be given to establishing consensus on the management of SLE-PAH-associated pregnancies in future studies.

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Contributors JZ, YS, ML, JL and XZ conceived and designed this study. ML, JQ, CH, QW, ZT and XT enrolled the patients, collected and analysed the data, and wrote the manuscript. Guarantor: JZ. All authors have read and approved this final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants but was not approved and does not contain personal and medical information about an identifiable individual. All participants gave informed consent to participate in the study before taking part.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Search Terms:

(pulmonary arterial hypertension[Title] OR pulmonary hypertension[Title] OR PAH[Title] OR PH[Title]) AND (pregnan*[Title] OR obstetr*[Title])

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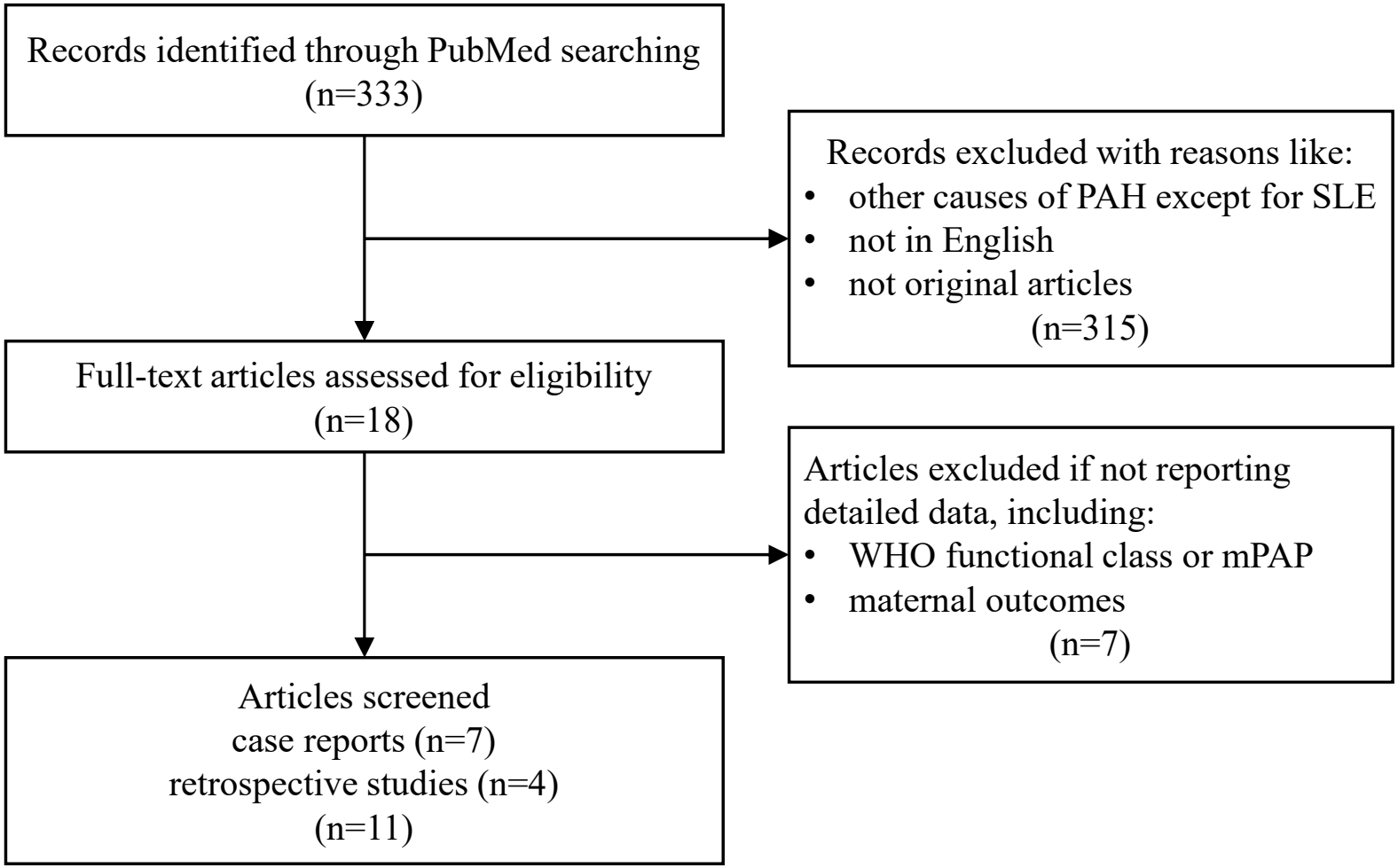

SLE, systemic lupus erythematosus; **PAH**, pulmonary arterial hypertension; **mPAP**, mean pulmonary artery pressure.

Supplementary Table 1 SLE- and PAH-specific medications and supportive treatments around pregnancy

		CS	Immunosuppressive agents						Target therapy			Supportive treatments			
			CTX	HCQ	TAC	AZA	LEF	MMF	PDE-5I	ERA	P	Inotropic	Diuretics	Aspirin	Anticoagulants
Planned pregnancy															
3#	Before pregnancy	√		√	√									√	√
	During pregnancy	√		√	√									√	√
	6 months after delivery	√		√	√						√				
9#	Before pregnancy	√		√											
	During pregnancy	√		√							√		√		
	6 months after delivery	√	√	√							√	√	√		
Unplanned pregnancy															
5#	Before pregnancy	√		√		√								√	√
	During pregnancy	√		√		√								√	√
	6 months after delivery	√		√		√							√	√	√
PAH developed during pregnancy															
1#	Before pregnancy	√													
	During pregnancy														
	6 months after delivery	√	√						√	√	√	√	√		√
2#	Before pregnancy														
	During pregnancy	√	√						√						√
	6 months after delivery	√	√	√					√		√			√	√
4#	Before pregnancy	√		√											
	During pregnancy	√		√											
	6 months after delivery	√	√						√	√		√	√		√
6#	Before pregnancy														

	During pregnancy	√					√							
	6 months after delivery	Death												
7#	Before pregnancy													
	During pregnancy	√							√					
	6 months after delivery	√	√						√	√	√			
8#	Before pregnancy													
	During pregnancy	√		√								√		
	6 months after delivery	√		√				√						
10#	Before pregnancy	√		√										
	During pregnancy	√		√										
	6 months after delivery	√	√	√					√					

SLE, systemic lupus erythematosus; **PAH**, pulmonary arterial hypertension; **CS**, corticosteroid; **CTX**, cyclophosphamide; **HCQ**, hydroxychloroquine; **TAC**, tacrolimus; **AZA**, acetazolamide; **LEF**, leflunomide; **MMF**, mycophenolate mofetil; **PDE-5I**, phosphodiesterase-5 inhibitor; **ERA**, endothelin receptor antagonist; **P**, prostacyclin analogs and prostacyclin receptor agonist.