


Effectiveness of a multidisciplinary clinical pathway for women with systemic lupus erythematosus and/or antiphospholipid syndrome

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ABSTRACT

Objectives SLE and/or antiphospholipid syndrome (SLE/APS) are complex and rare systemic autoimmune diseases that predominantly affect women of childbearing age. Women with SLE/APS are at high risk of developing complications during pregnancy. Therefore, clinical practice guidelines recommend that patients with SLE/APS should receive multidisciplinary counselling before getting pregnant. We investigated the clinical effectiveness of implementing a multidisciplinary clinical pathway including pre-pregnancy counselling of patients with SLE/APS.

Methods A clinical pathway with specific evaluation and pre-pregnancy counselling for patients with SLE/APS was developed and implemented in a tertiary, academic hospital setting. Patients were prospectively managed within the clinical pathway from 2014 onwards and compared with a retrospective cohort of patients that was not managed in a clinical pathway. Primary outcome was a combined outcome of disease flares for SLE and thromboembolic events for APS. Secondary outcomes were maternal and fetal pregnancy complications.

Results Seventy-eight patients with 112 pregnancies were included in this study. The primary combined outcome was significantly lower in the pathway cohort (adjusted OR (aOR) 0.20 (95% CI 0.06 to 0.75)) which was predominantly determined by a fivefold risk reduction of SLE flares (aOR 0.22 (95% CI 0.04 to 1.09)). Maternal and fetal pregnancy complications were not different between the cohorts (respectively, aOR 0.91 (95% CI 0.38 to 2.17) and aOR 1.26 (95% CI 0.55 to 2.88)).

Conclusions The outcomes of this study suggest that patients with SLE/APS with a pregnancy wish benefit from a multidisciplinary clinical pathway including pre-pregnancy counselling.

INTRODUCTION

SLE is a systemic autoimmune disease with an incidence of 8/100 000 predominantly diagnosed in women of childbearing age.^{1 2} Similarly, primary antiphospholipid syndrome (APS) is also diagnosed in women

Key messages

What is already known about this subject?

▶ Pregnancies in patients with SLE and/or antiphospholipid syndrome (APS) remain high-risk, therefore pre-pregnancy counselling is considered essential according to current international clinical practice guidelines.

What does this study add?

▶ This study establishes an approach to manage high-risk pregnancies in patients with SLE/APS by implementation of a multidisciplinary clinical pathway including pre-pregnancy counselling.
▶ Compared with a historical cohort, the implementation of such a clinical pathway significantly reduced a composite end point of disease-related flares (ie, SLE flares or thromboembolic events) during pregnancy.
▶ Pregnancy-related maternal and fetal outcomes were comparable in the historical cohort and clinical pathway cohort.

How might this impact on clinical practice or future developments?

▶ This study provides evidence that the implementation of a multidisciplinary clinical pathway including pre-pregnancy counselling can positively contribute to optimisation of the care for patients with SLE/APS with a pregnancy wish.

of childbearing age and characterised by venous or arterial thrombosis (thrombotic APS) or pregnancy complications (obstetric APS) in combination with the presence of antiphospholipid antibodies (aPL). Co-incidence of APS occurs in 20%–35% of patients with SLE and the overall incidence of APS is estimated to be around 5/100 000.^{3 4} As such, the desire to have children is a common issue for patients with SLE and APS and therefore a pregnancy wish should be addressed

as integral part of the management of patients with SLE and/or APS (SLE/APS).

From a maternal perspective, patients with SLE are at increased risk of flares and patients with APS are at increased risk of thromboembolic events (TEE) during pregnancy.^{5–6} Additionally, patients with SLE/APS are at higher risk of pregnancy complications such as gestational hypertensive disease (including pre-eclampsia and haemolysis elevated liver enzymes low platelets (HELLP) syndrome) and miscarriage. From a fetal/neonatal perspective, there is an increased risk for prematurity, fetal growth restriction (FGR), stillbirth and neonatal death. Also, infants born to SLE mothers who carry anti-Ro/SSA or anti-La/SSB antibodies have a 1%–2% risk of congenital heart block associated with neonatal lupus erythematosus.^{6–11}

As a consequence, some decades ago pregnancy was actually discouraged in women with SLE because of the potential severe pregnancy complications and disease exacerbations with pregnancy loss up to 43% in 1965.¹² Fortunately, increasing insights in the determinants that can negatively impact maternal and fetal outcomes, pregnancy loss in patients with SLE decreased to 17% in 2003.^{6–11–14} Consequently, pregnancies in patients with SLE are nowadays more and more embraced, rather than discouraged, taking into account the challenges in the management of pregnant patients with SLE/APS.^{15–17} This view is emphasised within the recently published Joint European League Against Rheumatism, European Renal Association and American College of Rheumatology (EULAR/ERA-EDTA/ACR) recommendations for the management of patients with SLE/APS with a pregnancy wish.^{18–20} Within these recommendations, preconception counselling is considered essential. It seems self-evident that prepregnancy counselling of patients with SLE/APS requires expertise from different specialisms and could therefore benefit from a multidisciplinary approach by a specialised team.^{21–22}

A strategy for implementation of a multidisciplinary approach for prepregnancy counselling of patients with SLE/APS is the use of a clinical pathway. While clinical practice guidelines have emerged as rigorous means to make clinical studies and research more accessible for practitioners, they are not always sufficient to change practice behaviour, especially in complex diseases such as SLE/APS.²³ Therefore, clinical pathways are an important strategy to improve effective knowledge transfer and sharing, promote standardised evidence-based practices and are internationally recognised as a form of quality improvement.^{23–24} Thus, based on EULAR/ERA-EDTA/ACR recommendations to implement multidisciplinary prepregnancy counselling for patients with SLE/APS, the present study investigated the clinical effectiveness of a clinical pathway with specific evaluation and prepregnancy counselling for patients with SLE/APS.

MATERIALS AND METHODS

Study design and participants

We performed a retrospective analysis of patients with SLE/APS that were prospectively managed in a multidisciplinary clinical pathway focused on prepregnancy counselling at a third-line, academic, referral centre compared with a cohort of patients with SLE/APS that were managed without a clinical pathway. Patients were included in the study over the period of January 2008 to February 2020. In 2014, a multidisciplinary clinical pathway was implemented involving specialists from the Department of Obstetrics, Rheumatology, Nephrology and Thrombosis and Haemostasis at the Leiden University Medical Centre (LUMC). On indication, a pulmonologist, cardiologist, radiologist and social worker were consulted. The study included SLE/APS pregnancies that were managed within the clinical pathway from May 2014 onwards (hereafter referred to as the ‘pathway cohort’) and pregnancies that were managed within our centre before initiation of the clinical pathway (hereafter referred to as ‘historical cohort’). Patients had to meet the following inclusion criteria: any singleton or multiple pregnant woman with a diagnosis of SLE according to the EULAR/ACR revised criteria of 2019 and/or an APS diagnosis according to the Sydney criteria.^{25–26} There were no exclusion criteria. The clinical pathway is described in more detail in the online supplemental file.

Management in the clinical pathway

Patients with SLE/APS with a pregnancy wish were enrolled in the clinical pathway from 2014 onwards. During the first visit, patients consulted the individual specialists of the multidisciplinary team in 2 days, with the guidance of a dedicated nurse. The multidisciplinary team included specialists from the Department of Obstetrics, Nephrology, Rheumatology and Thrombosis and Haemostasis at the LUMC. On indication, a pulmonologist, cardiologist, radiologist and social worker were consulted. Every 2 weeks all enrolled patients, before and during pregnancy, were discussed in a multidisciplinary meeting. At this meeting, a personalised, overarching, advice was formed concerning timing of pregnancy, medication policy and complementary medical check-ups and diagnostics for every new patient. Medication policy was established in accordance with guidelines on medication use during pregnancy and lactation.^{27–29} Figure 1 displays the possible content of the overarching advice in more detail, whereas specific prepregnancy counselling contents at first presentation are shown in online supplemental table S1. One week after the first visit, the women received elaborate counselling and advice. Obstetric routine ultrasound follow-up was advised for all patients: a 10–14 weeks ultrasound, an anomaly scan at 20 weeks of gestation and complementary ultrasounds at 24–28–32–36 weeks of gestation to monitor fetal growth. When patients were positive for anti-RO/SSA or anti-LA/SSB, weekly screening for congenital heart block in the framework of neonatal lupus was performed between week 18

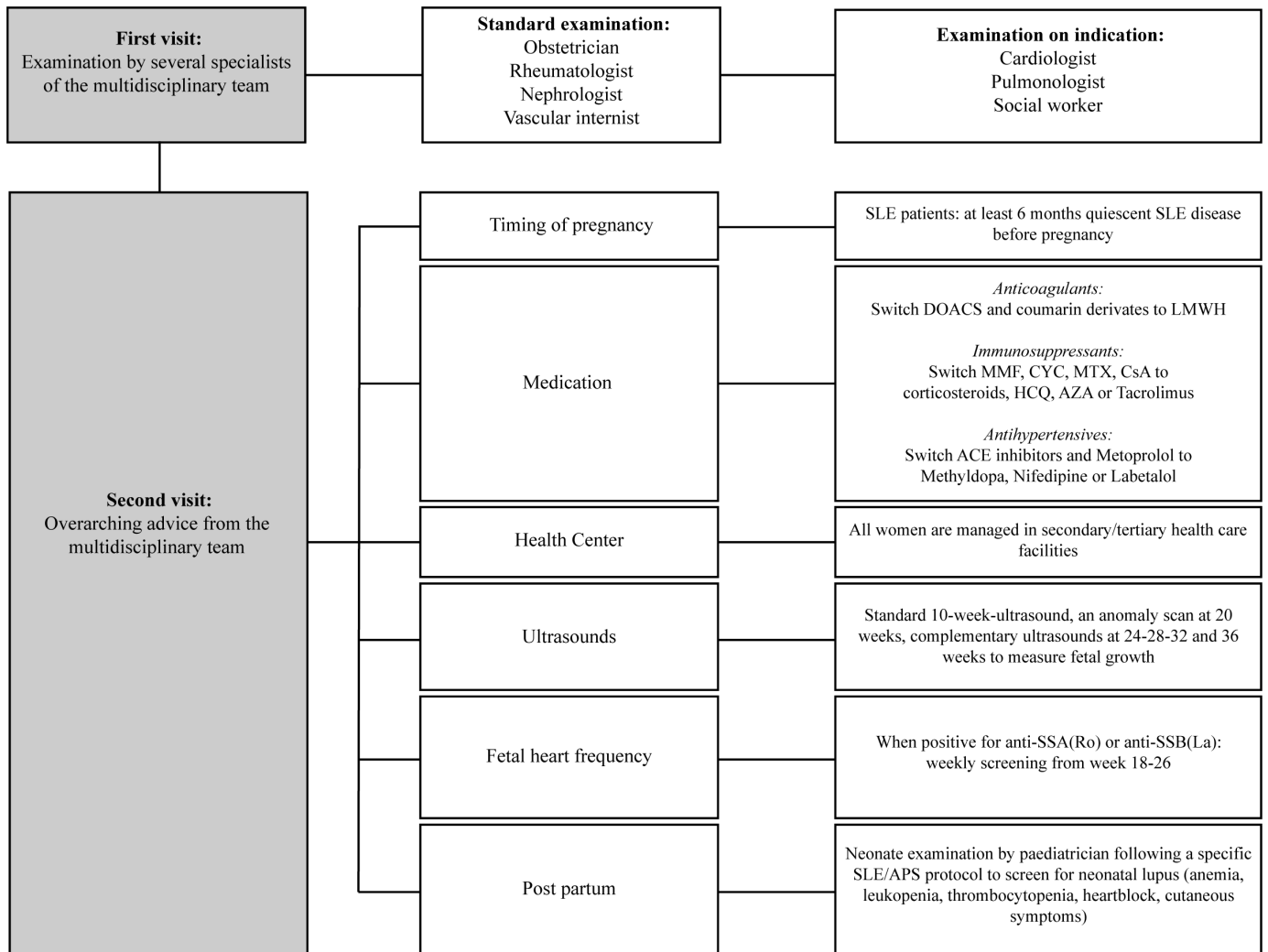


Figure 1 Management in the clinical pathway. APS, antiphospholipid syndrome; AZA, azathioprine; CsA, ciclosporin A; CYC, cyclophosphamide; DOACS, direct oral anticoagulants; HCQ, hydroxychloroquine; LMWH, low-molecular-weight heparin; MMF, mycophenolate mofetil; MTX, methotrexate.

and 26 weeks of gestation. For postpartum patients with SLE, paediatricians performed neonate examinations to screen for neonatal lupus. Furthermore, all women in the pathway were advised to use 80 mg acetylsalicylic acid daily, from the moment of a detected heartbeat around 8 weeks until 36 weeks of gestation. Low-molecular-weight heparin (LMWH) was indicated according to risk factors as is explained extensively in online supplemental table S2.

Data collection and outcomes

Data collection from electronic patient records included: disease-relevant maternal characteristics, obstetric characteristics, disease-relevant SLE/APS history and medication use.

The primary outcome was a combined end point of disease flares for patients with SLE and TEEs for patients with APS. SLE flares were defined as a combination of clinical symptoms, laboratory findings (complement consumption), treating physician's judgement of a disease flare and the initiation or intensification of

immunosuppressive treatment during pregnancy and the postpartum period (≤ 6 weeks post partum). Major flares were defined as those that involve central nervous system, kidney, lung, vasculitis, myositis, haemolytic anaemia with haemoglobin < 8 g/dL, thrombocytopenia $< 20\,000/\text{mm}^3$, addition of prednisone at doses > 0.5 mg/kg/day or addition of an immunosuppressive agent. All other flares are considered minor flares. Disease activity was established according to the Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI).³⁰ TEEs were defined as arterial, venous and small vessel thrombosis, other than superficial venous thrombosis, in any tissue or organ.

Secondary outcomes were defined as maternal and fetal outcomes: maternal outcomes included miscarriage (early miscarriage was defined as spontaneous pregnancy loss before 10 weeks and late miscarriage between 10 and 16 weeks of gestation), gestational hypertension and severe hypertensive disease including pre-eclampsia (systolic blood pressure ≥ 140 mm Hg and/or diastolic

blood pressure ≥ 90 mm Hg measured two times and proteinuria ≥ 300 mg/24 hours), eclampsia and HELLP syndrome. Fetal outcomes included perinatal death (fetal death ≥ 24 weeks of gestation or neonatal death ≤ 7 days post partum), FGR (birth weight < 10 th percentile of the PERINED 2008 dataset), congenital heart block (conduction system disease of the heart which is diagnosed antenatally or within 28 days after birth) and preterm birth (delivery before 37 weeks of gestation).

Statistical methods

The baseline characteristics and outcomes were summarised within the APS and the SLE pregnancies using descriptive statistics and comparisons between the pathway and historical cohort were analysed with Mann-Whitney U test for numerical and χ^2 test for categorical variables. Logistic regression with robust SEs to account for clustering of pregnancies within patients (Generalised Estimating Equations) was used to assess the association between the pathway and the primary and secondary outcomes. Disease characteristics at baseline and specific medical history were predefined as possible confounders for the association between attending the

clinical pathway and disease/pregnancy outcome. Predefined confounders were EULAR/ACR criteria points and a history of lupus nephritis for patients with SLE; and a history of lupus nephritis, TEE, pre-eclampsia and number of miscarriages for the combined analysis of patients. The small number of events did not allow correction for confounders in the separate analysis of the patients with primary APS. Adjusted ORs are presented from multivariable logistic regression analyses including these possible confounders. Statistical analysis was performed using SPSS V.25.0 software.

RESULTS

Participants

Seventy-eight patients with 112 pregnancies met the inclusion criteria (figure 2). In the pathway cohort, 30 patients with 41 pregnancies were included, 12 patients with SLE (\pm secondary APS) with 16 pregnancies and 18 patients with primary APS with 25 pregnancies. As illustrated in figure 2, 32 patients in the pathway cohort were awaiting pregnancy at time of analysis, of which 25 patients with SLE and 7 patients with primary APS. Of these 32 patients

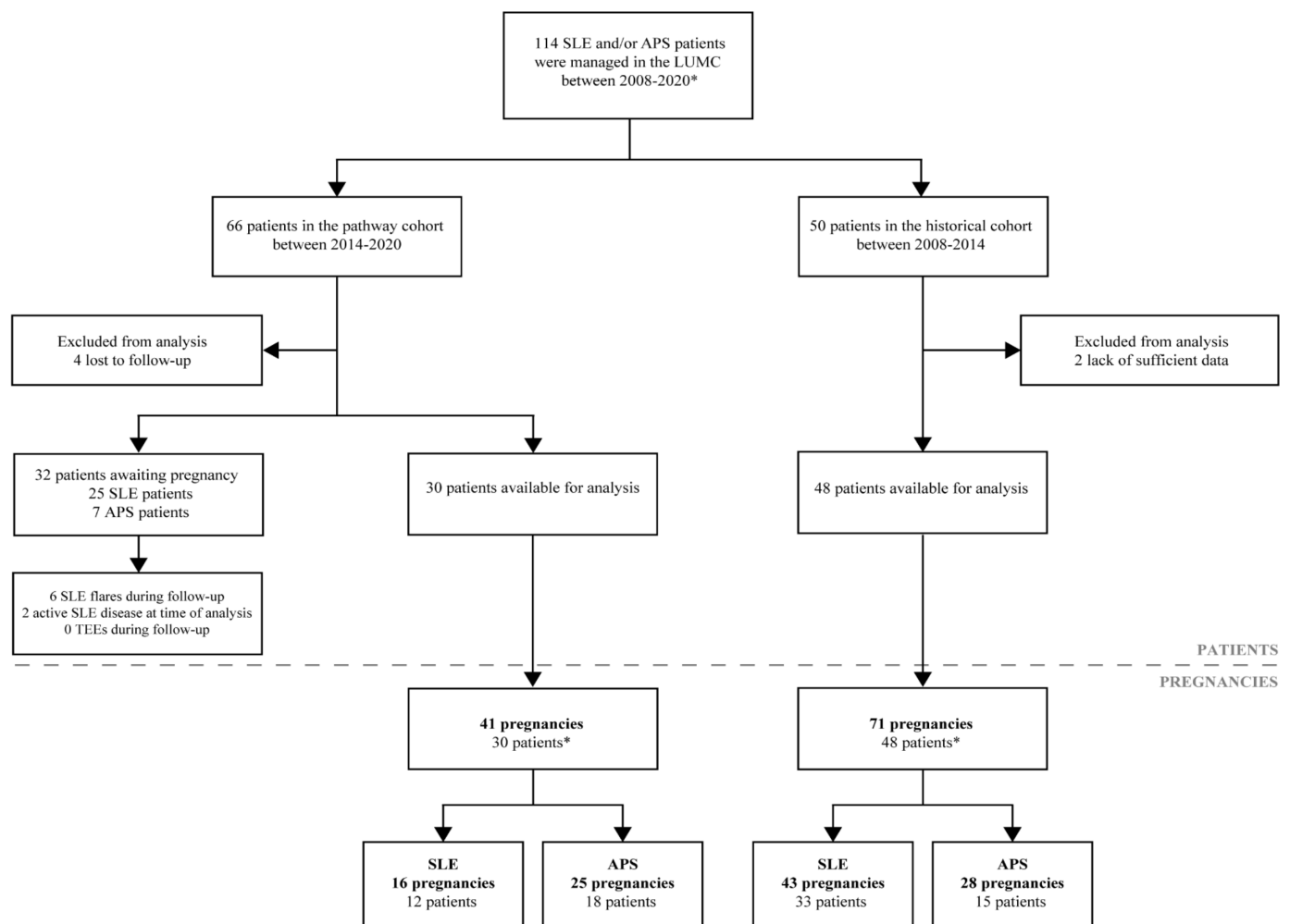


Figure 2 Flow chart of patient enrolment in the 'pathway' and 'historical' cohort. APS, antiphospholipid syndrome; LUMC, Leiden University Medical Centre; TEE, thromboembolic event. *Patients could be enrolled with multiple pregnancies.

awaiting pregnancy, 6 patients flared during follow-up (4 major, 2 minor flares), 2 patients had active disease at time of analysis and were advised to postpone conception until stable disease for >6 months was achieved. One patient conceived against medical advice (see online supplemental table S1 and S3 for disease characteristics of all patients and pregnancies in the pathway cohort).

In the historical cohort, 48 patients with 71 pregnancies were analysed, 33 patients with SLE (\pm secondary APS) with 43 pregnancies and 15 patients with primary APS with 28 pregnancies. Two patients overlapped as one pregnancy had follow-up in the pathway cohort, while the other received care in the historical cohort. Six patients were excluded from analysis due to lack of sufficient data and follow-up.

Descriptive data

As shown in [table 1](#), overall, for patients with SLE the median disease duration was 9 (5–11) years with a Systemic Lupus International Collaborating Clinics index score of 0 (0–1) that did not differ between the pathway and historical cohort. Patients with SLE in the pathway cohort had a significantly higher score on the item list of EULAR/ACR 2019 criteria, increased frequency of secondary APS and significant higher steroid dosing before pregnancy than in the historical cohort. Furthermore, the pathway cohort included numerically more women with a history of lupus nephritis (63% vs 47%) than the historical cohort, more often displayed complement usage at start of pregnancy and were more often treated with hydroxychloroquine and tacrolimus.

For patients with APS, the pathway cohort had a significantly higher frequency of women with obstetric APS and a history of miscarriages than the historical cohort. Furthermore, numerically fewer women with thrombotic APS were observed in the pathway cohort (32% vs 43%) with significantly less TEEs in medical history. Moreover, the women in the pathway cohort were less often triple-positive for the aPL than the women in the historical cohort. Interestingly, LMWH use in pregnancy was comparable.

Main results

The primary outcome of disease-related events was significantly reduced in the pathway cohort compared with the historical cohort (respectively 7% vs 28%, [figure 3](#)). The positive effect in the pathway cohort was mainly determined by a significant reduction in SLE flares (13% vs 40%, [table 2](#)). The crude OR for the disease outcomes composite was 0.20 (95% CI 0.06 to 0.73) in favour of the pathway cohort. After correction for predefined confounders, adjusted OR was 0.20 (95% CI 0.06 to 0.75). The crude OR for SLE flares was 0.22 (95% CI 0.05 to 1.05) and 0.26 (95% CI 0.03 to 2.22) for TEEs in primary APS pregnancies, both in favour of the pathway cohort. After adjustment, the OR for SLE flares had a tendency towards a reduced frequency in the pathway cohort, although the result was not statistically significant, 0.22 (95% CI 0.04 to

1.09). The SLEPDAI was 7 (minimum 6 to maximum 8) and 4 (2–16), respectively for SLE flares in the pathway compared with the historical cohort. One patient in the pathway (4%) and three in the historical (11%) cohort suffered from a TEE. Three of these patients did not use LMWH at the time of the TEE. Also, three out of four patients were triple-positive for the aPL.

With respect to secondary outcomes, both maternal and fetal outcome composites were not significantly different (respectively, adjusted OR 0.91 (95% CI 0.38 to 2.17) and 1.26 (95% CI 0.55 to 2.88)). Incidence of severe hypertensive disease did not differ significantly between the pathway cohort and the historical cohort for both SLE (31% vs 33%) and APS (27% vs 29%). In SLE pregnancies, the number of preterm births was comparable between the cohorts (38%). One case of congenital heart block was observed in the historical cohort needing implantation of a permanent epicardial pacemaker after birth. For patients with primary APS, preterm birth was seen more often in the pathway cohort than the historical cohort (40% vs 21%), although not significant. There were no differences in mode of delivery between the cohorts with a mean caesarean rate of 39%.

DISCUSSION

We are the first to demonstrate beneficial effects of the implementation of a multidisciplinary clinical pathway including prepregnancy counselling of patients with SLE/APS on pregnancy complications. This is to our knowledge the only comparative study that demonstrated a significant reduction in maternal-related complications in patients with SLE/APS that were managed within a clinical pathway. Notably, an almost fivefold reduction in SLE disease flares during pregnancy was achieved. Therefore, in addition to previous studies that extensively demonstrated the benefit of preconception counselling and timing of pregnancy, our study described an added-value managing pregnancies of patients with SLE/APS by a structured, multidisciplinary approach in a clinical pathway.^{15–22 31} Thus, our study establishes an approach to preconception counselling of patients with SLE/APS that is considered essential according to current international clinical practice guidelines.¹⁹

The present study investigated the implementation of a structured, multidisciplinary clinical pathway focused on patients with SLE/APS in the setting of an academic, referral centre. For this patient group with rare disease, evaluating the impact of implementation strategies is often challenging due to many unintended effects that occur by merely changing standard practice. Illustrative are the differences in baseline characteristics in our study where implementation of the clinical pathway may have led to the management of patients with SLE with higher grade of disease, less favourable disease characteristics and a higher number of patients with recurrent miscarriages due to obstetric APS. As such, it is very plausible that the implementation of a clinical pathway influences

Table 1 Baseline and disease characteristics in SLE and APS pregnancies

Pregnancies (n)	SLE		Primary APS	
	Pathway N=16	Historical N=43	Pathway N=25	Historical N=28
Maternal characteristics				
Age at conception*	33 (31–35)	32 (27–34)	31 (30–37)	30 (28–34)
Caucasian	11 (68.8)	29 (67.4)	18 (72.0)	14 (50.0)
Smoking during pregnancy	1 (6.3)	1 (2.3)	3 (12.0)	3 (10.7)
BMI (kg/m ²)*	24.9 (23.2–29.2)	23.5 (21.5–25.8)	26.2 (21.4–31.6)	25.9 (19.6–28.3)
Chronic hypertension	4 (25.0)	6 (14.0)	2 (8.0)	0 (0.0)
Obstetric characteristics				
Nulliparous	12 (75.0)	21 (48.8)	17 (68.0)	12 (42.9)
Singleton pregnancy	16 (100.0)	42 (97.7)	24 (96.0)	27 (96.4)
History of miscarriage	2 (12.5)	9 (20.9)	22 (88.0)†	16 (57.1)
History of pre-eclampsia	2 (12.5)	7 (16.3)	4 (16.0)	6 (21.4)
Specific APS history				
Thrombotic APS	3 (18.8)	1 (2.3)	78 (32.0)	12 (42.9)
Obstetric APS	1 (6.3)	1 (2.3)	14 (56.0)†	5 (17.9)
Thrombotic and obstetric APS	0 (0.0)	0 (0.0)	3 (12.0)†	11 (39.3)
History of thromboembolic events	4 (25.0)	6 (14.0)	10 (40.0)†	23 (82.1)
Lupus anticoagulant	5 (31.3)	3 (7.0)	15 (60.0)	23 (82.1)
Anticardiolipin antibodies	4 (25.0)†	0 (0.0)	10 (40.0)†	24 (85.7)
Anti-β2-glycoprotein-I antibodies	3 (18.8)	0 (0.0)	12 (48.0)	14 (77.8)
Number of positive aPL tests				
1	6 (37.5)†	3 (7.0)	14 (56.0)†	5 (17.9)
2	0 (0.0)	0 (0.0)	10 (40.0)	11 (39.3)
3	2 (12.5)	0 (0.0)	1 (4.0)†	12 (42.9)
Specific SLE history				
Duration SLE disease (years)*	9 (6–11)	9 (4–12)	–	–
SLICC damage index*	0 (0–1)	0 (0–1)	–	–
EULAR/ACR criteria*	23 (12–38)†	17 (10–22)	–	–
Secondary APS	4 (25.0)†	2 (4.7)	–	–
Serological Active Clinically Quiescent	3 (18.8)	0 (0.0)	–	–
Clinically active SLE <6 months before	1 (6.3)	4 (9.3)	–	–
History of LN				
I	0 (0.0)	2 (4.7)	–	–
II	0 (0.0)	1 (2.3)	–	–
III	2 (12.5)	3 (7.0)	–	–
IV	5 (31.3)	9 (20.9)	–	–
V	2 (12.5)	5 (11.6)	–	–
ANA				
Anti-Ro/SS-A	11 (68.7)	23 (53.5)	–	–
Anti-La/SS-B	4 (25.0)	13 (30.2)	–	–
Anti-dsDNA	7 (43.8)	18 (41.9)	–	–
Low C3 before pregnancy‡	8 (50.0)	8 (18.6)	–	–
Low C4 before pregnancy‡	4 (25.0)	3 (7.0)	–	–
Medication before pregnancy				

Continued

Table 1 Continued

Pregnancies (n)	SLE		Primary APS	
	Pathway N=16	Historical N=43	Pathway N=25	Historical N=28
Only HCQ or no immunosuppressants	3 (18.8)	21 (48.8)	25 (100.0)	28 (100.0)
Corticosteroid	11 (68.8)	18 (41.9)	–	–
Dose in mg*	10.0 (7.5–10.0)†	5 (4.4–8.1)		
Hydroxychloroquine	16 (100.0)†	25 (58.1)	2 (8.0)	1 (3.6)
Dose in mg*	350 (200–400)	400 (200–400)	400 (400–400)	400 (400–400)
Tacrolimus	7 (43.8)†	1 (2.3)	–	–
Dose in mg*	6 (4–6)	3 (3)		
Azathioprine	7 (43.8)	14 (32.6)	–	–
Dose in mg*	150 (100–150)	100 (50–125)		
Medication in pregnancy				
LMWH	4 (25.0)†	4 (9.3)	21 (84.0)	20 (71.4)
Acetylsalicylic acid	16 (100.0)†	22 (51.2)	21 (84.0)†	16 (57.1)

Data depicted as numbers (%) unless otherwise specified.

*Median (IQR).

†Shows a significant difference with two-sided $\alpha < 0.05$.

‡Low C3 defined as < 0.9 g/L and low C4 defined as < 95 mg/L

ACR, American College of Rheumatology; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; BMI, body mass index; dsDNA, double stranded DNA; EULAR, European League Against Rheumatism; HCQ, hydroxychloroquine; LMWH, low-molecular-weight heparin; ; LN, lupus nephritis; SLICC, Systemic Lupus International Collaborating Clinics; triple-positive, positivity for lupus anticoagulant+anti cardiolipin+anti- $\beta 2$ -glycoprotein 1.

physicians' decision to refer patients to that pathway. Nevertheless, even though the patients in the pathway cohort may have been skewed towards more severe SLE disease characteristics, maternal disease outcomes were improved without negative effects on the course of pregnancy. Implementation of the pathway, unfortunately, neither led to decreased pregnancy complications, which is likely associated with the disease characteristics at baseline. Also, for patients with APS, where more patients with thrombotic APS and triple aPL positivity were included in

the historical cohort, there was no significant difference observed in TEEs. The incidence of 8% TEE was comparable to the EUROAPS study however.³² Altogether, it remains noteworthy to establish the high incidences of pregnancy and disease complications in patients with SLE/APS, that is, flares, TEEs, severe hypertensive disease, preterm birth and FGR, re-affirming the need of specialised care in a tertiary, academic centre.

Current standard practice on prepregnancy counselling often relies on peer consultation in (pre-)pregnancy,

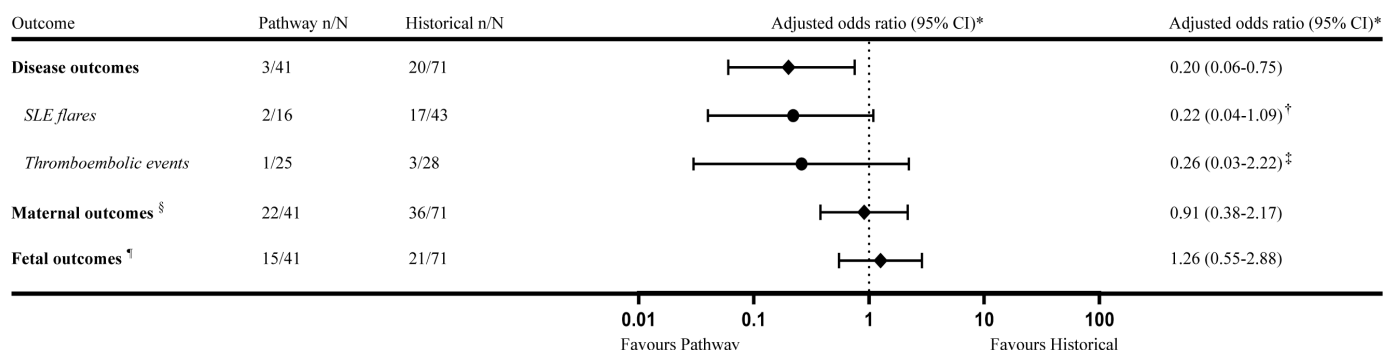


Figure 3 Composite outcomes comparing the pathway with the historical cohort. Data depicted as number of pregnancies.

*GEE model adjusted for predefined confounders: history of lupus nephritis, thromboembolic events, pre-eclampsia and the number of miscarriages.†GEE model adjusted for predefined confounders: lupus nephritis and EULAR/ACR criteria. ‡Crude OR was presented: the small number of events did not allow adjustment for confounders in the separate analysis of the patients with primary APS. §Composite outcome including miscarriage, gestational hypertension and severe hypertensive disease. ¶Composite outcome including perinatal death, fetal growth restriction, congenital heart block, preterm birth < 37 weeks, NICU admission. ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; GEE, Generalised Estimating Equations; NICU, neonatal intensive care unit.

Table 2 Primary and secondary outcomes for patients with SLE/APS in both cohorts

Pregnancies (n)	SLE (±secondary APS)		Primary APS (thrombotic+obstetric)	
	Pathway N=16	Historical N=43	Pathway N=25	Historical N=28
Disease outcomes				
SLE flare	2 (12.5)	17 (39.5)	–	–
Major SLE flare	1 (6.3)	7 (16.3)	–	–
Kidney	0/1 (0.0)	6/7 (85.7)	–	–
Heart/Lungs	1/1 (100.0)	0/7 (0.0)	–	–
Nervous system	0/1 (0.0)	0/7 (0.0)	–	–
Haematological	0/1 (0.0)	2/7 (28.6)	–	–
Minor SLE flare	1 (6.3)	10 (23.3)	–	–
Joints	1/1 (100.0)	8/10 (80.0)	–	–
Skin	0/1 (0.0)	4/10 (40.0)	–	–
SLEPDAI*	7 (6–8)	4 (2–16)	–	–
Thromboembolic events	0 (0.0)	0 (0.0)	1 (4.0)	3 (10.7)
Maternal outcomes				
Miscarriage	0 (0.0)	3 (7.0)	10 (40.0)	14 (50.0)
<10 weeks	0 (0.0)	3 (7.0)	10 (40.0)	9 (32.1)
10–16 weeks	0 (0.0)	0 (0.0)	0 (0.0)	5 (17.9)
Gestational hypertension†	1 (6.3)	2 (5.0)	2 (13.3)	0 (0.0)
Severe hypertensive disease‡	5 (31.3)	13 (32.5)	4 (26.7)	4 (28.6)
Vaginal delivery†	11 (68.8)	25 (62.5)	7 (46.7)	9 (64.3)
Fetal outcomes				
Perinatal death†	1 (6.3)	1 (2.5)	0 (0.0)	0 (0.0)
FGR (EFW <p10)†	3 (18.8)	8 (20.0)	1 (6.7)	1 (7.1)
Preterm birth <37 weeks†	6 (37.5)	15 (37.5)	6 (40.0)	3 (21.4)
Preterm birth <32 weeks†	1 (6.3)	5 (12.5)	1 (6.7)	2 (14.3)
Congenital heart block†	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)
NICU admission†	2 (12.5)	7 (17.5)	1 (6.7)	2 (14.3)

Data depicted as number of pregnancies (% of cohort).

Severe hypertensive disease=pre-eclampsia, eclampsia or HELLP.

*Median (minimum, maximum).

†For calculations miscarriages were excluded.

APS, antiphospholipid syndrome; EFW, estimated fetal weight; FGR, fetal growth restriction; HELLP, haemolysis elevated liver enzymes low platelets; NICU, neonatal intensive care unit; ; SLEPDAI, Systemic Lupus Erythematosus Pregnancy Disease Activity Index.

sometimes spread out over different hospitals, similar to the standard practice in the historical cohort of our study. We emphasised a more structured approach for these rare, often complex patients, starting before conception. Therefore, we organised a clinical pathway with a follow-up meeting every 2 weeks that provides an integral, patient-tailored treatment plan for the preconception, pregnancy, delivery and postpartum period based on the expert opinion of a multidisciplinary team. The multidisciplinary setting of the clinical pathway facilitated knowledge transfer, made interdisciplinary dialogue accessible, determined key management issues on a per case basis and created a learning environment on state-of-the-art developments in management of patients with SLE/APS

during pregnancy. As such, a clinical pathway was hypothesised to improve pregnancy outcome of patients with SLE/APS.

Importantly, one of the strengths of this study is the effectiveness of the clinical pathway cohort evaluated on clinically relevant outcomes. This is in contrast to the majority of studies evaluating clinical pathways which focused on outcomes as cost issues or reduction in length of hospital stay.³³ Also, even though the study's sample size is small and patients were recruited over a 12-year period, significant improvement in disease outcome could be detected in favour of the clinical pathway. Since no exclusion criteria were used, and because the initiation of a clinical pathway within our hospital organisation

provided a unique opportunity to study an ‘experiment of nature’ within our care organisation, we believe the results of this study can be generalised to other hospitals.

An inevitable limitation of this study is its small sample size caused by the rarity of SLE/APS and the negative impact on patients’ pregnancy wish. Although the specific interventions and therapy regimens during pregnancy have not dramatically changed over time, one could argue that some knowledge was increased given temporal trends which could have led to improved management of patients with SLE/APS before and during pregnancy. Therefore, outcomes could have altered over time, besides implementing the clinical pathway. Another limitation of the study was the inability to detect differences on clinically important outcomes for primary APS pregnancies. Furthermore, patients with SLE who were also aPL carriers were not given heparin by protocol in the clinical pathway (online supplemental table S2). Given the recent literature, preconception risk stratification should include aPL profile and heparin may be recommended to those patients with a more severe phenotype.^{25 34} Also, the recurrence rate of miscarriages was not included in this study that mainly focused on relevant pregnancy outcomes. Lastly, one needs to recognise that this study was conducted in a single centre and therefore careful interpretation of its results is warranted because of confounding factors and single-centre Hawthorne effects.^{24 33} Indeed, randomised controlled multicentre studies would be ideal for evaluating the effectiveness of the implementation of a clinical pathway, however hardly feasible and unethical in the rare and complex group of patients with SLE/APS with a pregnancy wish.

To conclude, our study demonstrated that patients with SLE/APS could benefit from pre-pregnancy counselling in a multidisciplinary clinical pathway. The risk of developing a SLE flare was lower even though the pathway cohort skewed towards more severe SLE disease characteristics. One has to recognise that the results of an implementation study that relies on a historical comparator have the inherent limitation that improvements in managing high-risk pregnancies in women with SLE/APS can also reflect temporal trends of improving management. However, because a randomised controlled study setting seems hardly feasible, our study provides evidence that the implementation of a multidisciplinary clinical pathway including pre-pregnancy counselling could contribute to optimisation of the care for patients with SLE/APS with a pregnancy wish.

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Supplemental file

Table SI. Pre-pregnancy counselling content of SLE/APS pregnancies in pathway cohort

<i>Pregnancies (N)</i>	SLE (+/- secondary APS) <i>N = 16</i>	Primary APS (thrombotic + obstetric) <i>N = 25</i>
Timing of pregnancy		
Pregnant at first presentation *	3 (18.8)	1 (4.0)
Advised to postpone pregnancy at first presentation	4 (25.0)	0 (0.0)
Conceived against medical advice	1 (6.3)	0 (0.0)
Medication		
Switch anticoagulants to LMWH	2 (12.5)	9 (36.0)
Switch immunosuppressants	5 (31.3)	0 (0.0)
Switch antihypertensives	2 (12.5)	1 (4.0)
Acetylsalicylic acid pre-eclampsia prophylaxis	16 (100.0)	25 (100.0)
Health Center (follow-up after counselling)		
Second line health center	1 (6.3)	8 (32.0)
Third line health center	15 (93.8)	17 (68.0)
Ultrasounds		
20-week anomaly scan	16 (100.0)	25 (100.0)
Fetal growth monitoring	16 (100.0)	25 (100.0)
Fetal heart frequency		
Weekly screening (18-26 weeks)	11 (68.8)	1 (4.0)
Postpartum		
Consultation of pediatrician	16 (100.0)	25 (100.0)

Data depicted as number of pregnancies (% of cohort).

* Patients were referred by their treating physician to the clinical pathway after conception and did not receive preconception counselling in the clinical pathway

Table SII. LMWH policy in the clinical pathway

Disease characteristics	LMWH policy
SLE (+) aPL (-) thrombosis (-)	No indication for LMWH
SLE (+) aPL (+) thrombosis (-)	Postpartum period ^a
SLE (+) provoked thrombosis (+)	Postpartum period ^a
SLE (+) unprovoked thrombosis (+)	Pregnancy and postpartum period ^a
Obstetric APS: ≥ 3 consecutive miscarriage < 10 wks (+)	Pregnancy and postpartum period ^a
Obstetric APS: 1 or more premature birth ≤ 34 weeks due to placental insufficiency (+) / 1 or more fetal death ≥ 10 weeks (+)	Postpartum period ^a
Thrombotic APS (+) anticoagulants use pre-pregnancy (-)	Pregnancy and postpartum period ^a
Thrombotic APS (+) anticoagulants use pre-pregnancy (+)	Therapeutic LMWH dose depending on weight, kidney function and anti-Xa blood level during pregnancy and postpartum period

LMWH = Low-Molecular-Weight Heparin. SLE = systemic lupus erythematosus. aPL = antiphospholipid antibodies, APS = antiphospholipid syndrome.

^a Standard prophylactic LMWH dose is 2850 IU nadroparin. Postpartum period consists of 6 weeks. When a patient's weight was > 100 kg, a dose of 5800 IU nadroparin was prescribed.

Table SIII. Disease characteristics at first presentation of all SLE/APS patients in pathway cohort compared with historical cohort

Patients (N)	SLE patients		Primary APS patients	
	Pathway N = 37	Historical N = 33	Pathway N = 25	Historical N = 15
General characteristics				
Caucasian	21 (56.8)	22 (66.7)	16 (64.0)	9 (60.0)
BMI (kg/m ²) at first presentation ^β	24.1 (21.9-28.1)	23.5 (21.4-25.7)	26.2 (21.7-31.4)	26.0 (21.7-29.4)
Specific APS history				
Thrombotic APS	6 (16.2)	1 (3.0)	8 (32.0)	6 (40.0)
Obstetric APS	1 (2.7)	1 (3.0)	14 (56.0)	5 (33.3)
Thrombotic and obstetric APS	0 (0.0)	0 (0.0)	3 (12.0)	4 (26.7)
History of thromboembolic events	10 (27.0)	5 (15.2)	11 (44.0)	10 (66.7)
Lupus anticoagulant	8 (21.6)	3 (9.1)	16 (64.0)	10 (66.7)
Anticardiolipin antibodies	2 (5.4)	0 (0.0)	13 (52.0)	11 (73.3)
Anti-β2-glycoprotein-I antibodies	3 (8.1)	0 (0.0)	12 (48.0)	5 (33.3)
Triple positive	0 (0.0)	0 (0.0)	3 (12.0)	3 (20.0)
Specific SLE history				
SLICC damage index ^β	0 (0-2)	0 (0-1)
EULAR/ACR criteria ^β	21 (14-29)	18 (11-22)
Secondary APS	7 (18.9)	2 (6.1)
History of LN	17 (45.9)	15 (45.5)
ANA	33 (89.2) *	21 (63.6)
Anti-Ro/SS-A	15 (40.5)	16 (48.5)
Anti-La/SS-B	6 (16.2)	8 (24.2)
Anti-dsDNA	14 (37.8)	13 (39.4)

Data depicted as number of patients (% of cohort). SLE = Systemic Lupus Erythematosus. APS = antiphospholipid syndrome. BMI = Body Mass Index. Triple-positive = positivity for LAC + ACA + Anti-β2-GPI. SLICC = Systemic Lupus International Collaborating Clinics. LN = lupus nephritis. ANA = Anti-Nuclear Factor.

^β Median (IQR)

*Shows a significant difference with 2 sided $\alpha < 0.05$.

Table SIV. Crude and adjusted odds ratios comparing the pathway to the historical cohort

Pregnancies (N)	SLE and/or primary APS patients			
	Pathway n/N	Not in pathway n/N	Crude OR (95% CI)	Adjusted OR (95% CI)
Disease outcomes composite	3/41 (7.3)	20/71 (28.1)	0.20 (0.06-0.73)	0.20 (0.06-0.75) *
SLE flares (SLE pregnancies)	2/16 (12.5)	17/43 (39.5)	0.22 (0.05-1.05)	0.22 (0.04-1.09) ^μ
TEEs (APS pregnancies)	1/25 (4.0)	3/28 (10.7)	0.26 (0.03-2.22)	.. [¶]
Maternal outcomes composite [¥]	22/41 (53.7)	36/71 (50.7)	0.98 (0.40-2.42)	0.91 (0.38-2.17) *
Fetal outcomes composite ^β	15/41 (36.6)	21/71 (29.6)	1.20 (0.53-2.71)	1.26 (0.55-2.88) *

Data depicted as number of pregnancies (% of cohort). SLE = systemic lupus erythematosus. TEEs = thromboembolic events

*GEE model adjusted for predefined confounders: history of lupus nephritis, thromboembolic events, pre-eclampsia, and the number of miscarriages.

^μ GEE model adjusted for predefined confounders: lupus nephritis and EULAR/ACR criteria.

[¶] The small number of events did not allow adjustment for confounders in the separate analysis of the primary APS patients.

[¥] Composite outcome including miscarriage, gestational hypertension and severe hypertensive disease.

^β Composite outcome including perinatal death, fetal growth restriction, preterm birth < 37 weeks, NICU admission.