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Susac syndrome and pregnancy: a review of published cases and considerations for patient management

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***Abstract*:** Susac syndrome (SuS) is a rare autoimmune endotheliopathy leading to hearing loss, branch retinal artery occlusions and encephalopathy. Young females are more frequently affected than males, making counselling for family planning an important issue. We reviewed published cases on SuS during pregnancy or in the postpartum period, and selected 27 reports describing the details of 33 patients with SuS. Treatment options and implications for pregnancy and breastfeeding are discussed. We propose new areas for research and suggest a management strategy.

Keywords: pregnancy, Susac syndrome

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Introduction

Susac syndrome (SuS) is named after John Susac, who was the first to describe the syndrome of encephalopathy, hearing loss and branch retinal artery occlusions (BRAO).[1,2] It is a rare disease, with just over 500 cases described worldwide.[3] Diagnostic criteria were proposed by the European Susac Consortium in 2016.[4] The pathophysiology of this neuroinflammatory disease, which affects the endothelial cells of microvessels in the brain, cochlea and retina, remains poorly understood. Activated cytotoxic CD8+ T-cells contribute to inflammatory damage of the endothelium. Anti-endothelial cell antibodies are present in 25% of patients, but their role in SuS pathogenesis is not clear.[5–7] Treatment is based on expert opinion and case-series as clinical trials are non-existent in this rare disease. A practical treatment guideline for SuS based on a single expert opinion has been proposed recently, offering different therapeutic regimens for milder to more severe forms of the disease.[8] Less aggressive treatment recommendations have been made by others.[9]

SuS affects young women more frequently than men, with a female:male ratio of 3.5:1.[10] It is not surprising that, in the age category affected, family planning is often not completed, making counselling necessary. Moreover, SuS can present for the first time, or relapse after a period of disease remission, during pregnancy or in the postpartum period.[10]

In this article, we review published cases of SuS during pregnancy and the postpartum period, discuss issues in family planning in SuS patients, suggest areas for further research and propose a management strategy.

Review of published cases

We searched the literature (Pubmed) and internet (Google) for published case reports, case series and review articles for descriptions of SuS patients during pregnancy, postpartum or after termination of pregnancy (search terms: Susac, pregnancy, postpartum; search until August 2020) and selected 27 reports describing a total of 33 SuS patients.[11–37] All cases are listed in Table 1. The mean age at pregnancy was 28.6 years. In 21 patients, the disease was diagnosed during pregnancy (five in the first trimester, seven in the second trimester, eight in the third trimester and one not reported) and in eight patients there were relapses during

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Table 1. Case reports, case series and review articles for descriptions of SuS patients during pregnancy, postpartum or after termination of pregnancy.

Case	SuS diagnosis before pregnancy	Age at diagnosis of SuS	Age at pregnancy	Gestational age or postpartum	Presenting symptoms	Audiometry	Ophtalmology	MRI	CSF	Treatment	Outcome	Pregnancy outcome	Reference	Prior symptoms and/or pregnancies
1	N	22	21	postpartum	headache and hearing impairment, confusion, personality change, unsteady gait	bilateral hearing loss	Fundoscopy: cotton-wool spots FA: multiple BRAO bilateral		increased protein (187 mg/dl)	steroids	remarkable improvement	stillbirth at term (anencephalic child)	Coppeto 1984	delivery of a healthy child 6 years prior; first symptoms started the month before pregancy, with personality change and high protein levels in CSF
2	N	31	31	first trimester	numbness in the extremities, segmental visual loss, diplopia, lethargy, memory loss, change in personality, dysarthria, gait unsteadiness, tinnitus, and hearing loss	bilateral low frequency SNHL, left more than right	Fundoscopy: retinal arteriolar occlusions		0 wbc/µl increased protein (252 mg/dl) OCB absent	no treatment	speech, memory, gait, personality improved	healthy baby	MacFadyen 1987	3 prior pregnancies
2				postpartum	sudden deterioration left hearing, fatigue, dysarthria, incoordination in writing and gait, memory problems		Fundoscopy: small intraretinal hemorrhages, adjacent artery narrowing, perivascular sheathing and artery narrowing		0 wbc/µl increased protein (116mg/dl)	steroids	improvement speech, dizziness and memory, further visual loss	N/A	MacFadyen 1987	
3	N	28	28	28	sudden, painless visual loss right eye, periodic imbalance; deterioration over the next month with severe encephalopathy	mild bilateral SNHL	Fundoscopy: retinal arteriolar occlusion, cotton-wool spot	multifocal T2 hyperintensitiesintensity in the deep white matter, anterior corpus callosum, and brain stem	2 wbc/µl increased protein (207 mg/dl) OCB absent	heparin, warfarin followed by aspirin	gradual improvement after delivery in mental status and walking, persistent visual field deficits	pre-term (33 weeks gestation) healthy boy	Gordon 1991	no prior symptoms or pregnancies
4	N	36	36	immediately postpartum	visual loss, tetrapyramidal signs, confusion	right-sided hearing loss	Fundoscopy: normal	T2 hyperintensities in the supratentorial white matter and basal ganglia	6 wbc/µl increased protein (264 mg/dl)	during pregnancy: aspirin monotherapy until 26 weeks GA, thereafter low molecular weight heparin; after delivery oral anticoagulants	psychological sequelae and hearing loss despite treatment with hyperbaric oxygen	induction of delivery with prostaglandin gel a terme; urgent caesar section, delivery of healthy girl	Cador-Rousseau 2002	3 previous pregancies, of which 1 voluntary abortion, 1 spontaneous abortion and 1 at term pregnancy prior symptoms: 6 years prior sudden left, hearing loss, 2 years prior thrombosis of a branch of the right central retinal artery, 3 months prior to pregnancy thrombosis of a branch of the left central retinal artery

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Table 1. (Continued)

Case	SuS diagnosis before pregnancy	Age at diagnosis of SuS	Age at pregnancy	Gestational age or postpartum	Presenting symptoms	Audiometry	Ophtalmology	MRI	CSF	Treatment	Outcome	Pregnancy outcome	Reference	Prior symptoms and/or pregnancies
5	Y	35	35	pregnancy discovered during cyclophosphamide treatment (before 10 weeks GA)						steroids, anticoagulation,cyclophosphamide,aspirin		therapeutic abortion	Aubart-Cohen 2007	
6	N	25	25		behavioral disturbances		new retinal occlusions			steroids, anticoagulation		therapeutic abortion	Aubart-Cohen 2007	
6	Y	25	29	no relapse during pregnancy						aspirin		healthy baby at term	Aubart-Cohen 2007	
7	Y	30	33	postpartum	confusion, vertigo, and hearing loss					aspirin		healthy baby at term	Aubart-Cohen 2007	
8	N	28	28	37	confusion, forgetfulness, hypersomnolence, headaches, hearing difficulties, and episodic visual loss	low frequency SNHL	Fundoscopy: bilateral BRAO with retinal infarcts. FA: bilateral retinal infarcts, BRAO, and arteriolar hyperfluorescence	multiple T2 hyperintensities in the cerebellum and cerebral white matter, including corpus callosum. Many lesions were hypointense on T1-weighted imaging and some demonstrated restricted diffusion	3 wbc/µl increased protein (121 mg/dl)	aspirin, steroids (IV pulse and oral taper), IVIg, mycophenolate mofetil	Seven months postpartum: short-term memory problems,right eye visual problems, hearing loss in left ear, easy fatiguability	healthy baby girl	Grinspan 2009	4 previous pregnancies: 2 healthy children, 1 abruption at 23 weeks, and 1 electiveabortion
9	N	23	23	10 days after voluntary abortion	retro-bulbar headache, photophobia, vomiting andlethargy	bilateral low frequency SNHL	Fundoscopy and FAA: sporadic segmental retinalarterial occlusions in both eyes	multiple punctate foci of restricted diffusion and T2 hyperintensities in the deep white matter of both frontal lobes, a larger lesion in the splenium of the right corpus callosum	8 wbc/µl increased protein 183 mg/dl	steroids (IV pulse and oral taper), single dose of infliximab, IVIg, cyclophosphamide, aspirin, nifedipine; later cyclophosphamide stopped and switch to azathioprin	After twelve months: tinnitus and hearing loss persisted, cognition continued to improve, ongoing deficits in spontaneous recall, working memory and verbal fluency	voluntary termination of pregnancy at GA of 7 weeks	Hardy 2011	
10	N	25	25	20	confusion, difficulty walking, and vision and hearing loss, intermittent headaches	left-sided SNHL	Fundoscopy: left-sided BRAO and cotton wool spots FA not done	T2 hyperintensities in the deep and periventricular white matter, corpuscallosum, pons, and cerebellar peduncles; a 2-3 mm hypointense 'hole' in the midportion of the corpus callosum	16 wbc/µl increased protein (63 mg/dL)	steroids (IV pulse and oral taper), IVIg, aspirin	Improvement of mental status, gait, hearing and visual loss persisted		Deane 2011	

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Table 1. (Continued)

Case	SuS diagnosis before pregnancy	Age at diagnosis of SuS	Age at pregnancy	Gestational age or postpar-tum	Presenting symptoms	Audiometry	Ophtalmology	MRI	CSF	Treatment	Outcome	Pregnancy outcome	Reference	Prior symptoms and/or pregnan-cies
10				33	abrupt confusion and worsening gait, new bilateralhearing loss, and new right vision changes		Fundoscopy: retinal ischemia on the right	several new lesions		repeat IV steroids, IVIg, ;postpartum cyclophos-phamide and rituximab added; after 3 doses of cyclophos-phamide oral azathioprin	Significant improvement; development of livedo reticu-laris	induction of premature delivery at 35 weeks gestation; delivery of healthy baby girl	Deane 2011	
11	N	35	35	31	bilateral visual loss and right hearing loss, cognitive symptoms	SNHL right ear, left side normal	Fundoscopy: bilateral narrow-ing of arterioles punctiform hemorrhage FA: leakage in multi-ple arterioles in both eyes	supra- and infra-ten-torial T2 hyperintensi-ties in white matter	lymphocytic pleiocytosis increased protein OCB absent	steroid pulse; repeated ; plasma exchange; postpartum cyclophospha-mide, followed by mycophe-nolate; due to ongoing disease activ-ity changed to methotrexate and etaner-cept	Bilateral hear-ing loss, visual field defects; ongoing disease activity (retinal vasculitis) after pregnancy for 5 years	caesarean section, premature delivery of health baby boy	Finis 2011	
12	N	30	30	3 weeks postpartum	headache, hearing loss, attention deficit, personality and mental changes, impaired cognition and memory	SNHL, low and middle tones, right more than left side	Fundoscopy and FA: bilateral BRAO with retinal ischemia, arteri-olar shunts, and small vascular dilatations	small T2 hyperintensi-ties, atrophic corpus callosum	normal OCB absent	steroids (IV pulse and oral taper), aspirin, nimodipine	no recurrence after 6 months and 1 year; no improvement in hearing	normal baby	Karelle 2012	Three episodes of aseptic meningitis (age of 5, 14, and 27 years). Between these events,the patient suffered from migraine-like headache and atypical polyarthritis.
13	N	34	34	third trimester	Headaches,numbness andtingling ofhands and face,visual field-defect, hearingloss, tinnitus			T2 hyperintensities and corpus callosum involvement	2 wbc/µl increased protein (101 mg/dl)	steroids (oral) , aspirin, plas-mapheresis	postpartum symptoms stabilised, re-currence after steroid taper	not reported	Mateen 2012	
14	N	32	32	postpartum	Vertigo, diplopia,visual loss,tingling ofhands and feet,and amnesti-cepisodes	Low- to mid-frequency-SNHL		T2 hyperintensities and corpus callosum involvement , gadolini-um enhancement	11 wbc/µl increased protein (161 mg/dl) OCB absent	steroids (IV and oral), aspirin, plas-mapheresis	improved, later episodes of visual and hear-ing loss		Mateen 2012	

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Table 1. (Continued)

Case	SuS diagnosis before pregnancy	Age at diagnosis of SuS	Age at pregnancy	Gestational age or postpartum	Presenting symptoms	Audiometry	Ophtalmology	MRI	CSF	Treatment	Outcome	Pregnancy outcome	Reference	Prior symptoms and/or pregnancies
15	N	32	32	32	change in personality, unsteadiness of gait, slurred speech, evolving to severe disorientation and confusion			multiple small T2 hyperintensities in both supra- and infratentorial locations, some of which exhibited diffusion restriction, several of which in corpus callosum	13 wbc/µl increased protein (180 mg/dl) OCB absent	steroids (IV and oral), IVIG and mycophenolate and methotrexate	1 year after the diagnosis the patient was well with markedly improved gait and cognition	emergency caesarean section	Engeholm 2013	
16	N	28	28	9	lower limb weakness, drowsiness and dysarthria			T2 hyperintensities with an unusual pattern of meningeal enhancement after Gadolinium administration; serialMRI showed progressive lesions in the deep white matter, including the basal ganglia and cerebellar peduncles withenhancing lesion in the corpus callosum that progressed to volume loss	9 wbc/µl increased protein (200 mg/dl) OCB absent	steroids (IV pulse and oral taper), plasma exchange, IVIg	cognitive deficits persisted, hearing and vision remain impaired	at 13 weeks GA 1 viable fetus; therapeutic abortion at 15 weeks GA	Ioannides 2013	
17	N	21	21	35	walking impairment and evolving hearing loss, lack of concentration and disorientation	bilateral moderate low frequency SNHL in the low frequency range, left-more than right side	FA: normal	multiple small T2 hyperintensitiesin the corpus callosum, periventricular white matter, centrum semiovale, posterior arm of the left internal capsule, pons and cerebral peduncles; some lesions demonstrated restricted diffusion on DWI, as well as hypointensity on T1-weighted imaging	4 wbc/µl increased protein (109 mg/dl)	low-molecular-weight heparin, IVIg; after delivery start of oral azathioprine and warfarin	After two months: hearing loss persisted, discrete activity on FAAwithout functional visual impairment; no new symptoms; MRI showed new lesions	induction of labour at 37 weeks	Antulov 2014	
18	N	35	35	37	hearing loss and tinnitus in the left ear, attacks of vertigo and slight difficulty in finding words	mild hearing loss in theleft ear			normal OCB absent	postpartum: aspirin, steroids (IV and oral taper), cyclophosphamide	BRAO in the right eye 2.5 months after having given birth		Feresiadou 2014	At the age of 12: encephalopathy, sudden deafness of the right ear and visual field defects in the left eye at the age of 12, followed by permanent hearing and visual defects. Second pregnancy.

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Table 1. (Continued)

Case	SuS diagnosis before pregnancy	Age at diagnosis of SuS	Age at pregnancy	Gestational age or postpartum	Presenting symptoms	Audiometry	Ophtalmology	MRI	CSF	Treatment	Outcome	Pregnancy outcome	Reference	Prior symptoms and/or pregnancies
19	N	25	25	14	acute onset of right leg shooting pain, followed by complaints of vertigo, blurry vision, headache and gait instability; severe encephalopathy			multiple T2 hyperintensities in the bilatera lwhite matter, deep gray matter,corpus callosum and posterior fossa with corresponding restricted diffusion and T1 hypointensities for the observed corpus callosum lesions	6 wbc/µl increased protein (95 mg/dl)OCB absent	steroids (IV pulse) repeated approx.2 weeks later (oral) when symptoms reoccurred	One month postpartum: hearing difficulty (right sensorineural hearing loss), two months later cognitive difficulties. 1,5 years after initial presentation residual cognitive deficits consisting of visual spatial deficits and difficulty with word recall and vocabulary	healthy baby	Hua 2014	
20	N		25	11	confusion, short term memory loss, headache and uncoordinated gait			multiple periventricular and deep white matter T2 hyperintense lesions in a perpendicular distribution to the ventricles		steroids (pulse)		healthy baby	Tashman 2014	
20				24	repeated symptoms					steroids (pulse)			Tashman 2014	
20				3 months postpartum	confusion, headache, and lethargy	bilateral low frequency hearing loss, rising to normal at higher frequencies	bilateral BRAOs with retinal infarcts	small, multifocal T2 hyperintensities in the white matter involving the corpus callosum	increased protein	steroids (pulse), mycophenylate			Tashman 2014	
21	N		18	24	visual loss right eye, followed by severe headache	normal	No FA, central retinal artery occlusion	small T2 hyperintensities		steroids (pulse and oral taper), LMWH	symptom free in 4 days, except vision right eye; recurrence of disease activity 1 year after starting estrogen replacement therapy at the age of 50 years (Petty 2001)		Khan 2014	

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Table 1. (Continued)

Case	SuS diagnosis before pregnancy	Age at diagnosis of SuS	Age at pregnancy	Gestational age or postpartum	Presenting symptoms	Audiometry	Ophtalmology	MRI	CSF	Treatment	Outcome	Pregnancy outcome	Reference	Prior symptoms and/or pregnancies
22	Y		37	6 weeks postpartum	mild hearing loss right ear, visual aura		FA: BRAO with leakage			steroids (oral), azathioprine (azathioprine discontinued during pregnancy due to anemia)	full recovery	healthy baby	van der Kooij 2015	
23	N		29	8	right hearing loss, vertigo, and mild headache					steroids (oral, pulse)			London 2016	
23				19	left visual field deficit, headache		FA: bilateral multiple BRAO	multiple T2 hyperintensities in the deep white matter including the splenium of the corpus callosum and the left cerebellum	mildly elevated protein OCB absent	steroids (pulse and oral taper), antiplatelet therapy; cyclophosphamide 1 g every 4 weeks (initiated at 28 weeks gestational age, due to relapses)	persistent bilateral hypoacousia requiring hearing aid	healthy baby	London 2016	
23				postpartum	dizziness and visual loss			gadolinium-enhancing lesions		steroids (pulse)			London 2016	
24	N		21	3 months	visual and hearing loss; after curretage rapid onset of encephalopathy	no SNHL	Fundoscopy: retinal edema FA: leakage, no BRAO		increased protein	steroids (oral taper)	complete recovery 2 weeks later	missed abortion	Bhattu 2017	
25	N		25	7 months	visual loss left eye, hearing loss and tinnitus, mild headache	SNHL right ear	Fundoscopy: ischemic retinal edema inferotemporal and cherry-red spot	periventricular and callosal T2 hyperintensities	not reported	steroids (pulse and oral taper)	improvement in headache, some recovery of vision		Manik 2018	
26	N		19	14	headache, somniloquy	SNHL low frequencies	FA: multiple BRAO	multiple diffusion restrictive T2 hyperintensities, also in corpus callosum	increased protein OCB absent	steroids (pulse) and aspirin		no fetal anomaly	Can Usta 2018	

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Table 1. (Continued)

Case	SuS diagnosis before pregnancy	Age at diagnosis of SuS	Age at pregnancy	Gestational age or postpartum	Presenting symptoms	Audiometry	Ophtalmology	MRI	CSF	Treatment	Outcome	Pregnancy outcome	Reference	Prior symptoms and/or pregnancies
27	N		34	15	apathy and behavioral changes; vertigo 6 months prior and an episode of right ear tinnitus 2 months prior	bilateral SNHL	retinal vasculitis-corroborated by FA	hyperintense periventricular white matter lesions in T2 andFLAIR sequences also involving bilateral basal ganglia and with pre-dominant affection of the corpus callosum, in addition to infratentorialcerebellar lesions. Lesional restriction of diffusion but no contrast en-hancement was observed. T1 weighted images showed hypointenselesions in the same topography	CSF values showed proteins of 77 mg/dl,glucose of 52 mg/dl (serum glucose of 89 mg/dl), and no cells.	5 pulses of methylprednisolone were administeredwithout obvious clinical improvement. Immunomodulatory treatmentwas escalated to intravenous immunoglobulin (IVIg) at 0.4 g/kg/dayfor 5 days; prednisone orally and CCF after abortion	partial remission	therapeutic abortion	Gomez-Figueroa 2018	
28	Y	23	45		no relapse during pregnancy or postpartum					no treatment since 8 years, 2 years relapse free after delivery	IVF four cycles of GnRH antagonist, ganirelix	healthy twins at 35 weeks GA	Qiu 2020	
29	N	24	23	11 months postpartum	ataxia, vomiting, minor cognitive impairment and blurred vision in theright eye			T2 hyperintensities inthe deep and subcortical white matter, brainstem and cerebellumassociated with restricted diffusion, callosal snowball lesions	9wbc/μl increased protein 120 mg/dl	aspirin, steroids (pulse and oral taper), IVIg	After 1 month symptoms resolved, patient fell pregnant, resulting in a spontaneous miscarriage two months later.		Qiu 2020	
30	N		24	1 month post- spontaneous abortion	subacute severebilateral hearing impairment requiring hearing aids, and partial visualloss in the left eye	mild bilateral low frequency SNHL	FA: bilateral BRAOs	MRI six months postrituximab was stable		Steroids (oral), rituximab			Qiu 2020	
30	Y		25	22 months after initial presentation						11 months after last rituximab dose		healthy baby at 38 weeks	Qiu 2020	
31	N	34	34	7	moderate encephalopathy, vertigo	unilateral SNHL	bilateral	T2 hyperintensities in the supratentorial white and gray matter areas	14 wbc/μl increased protein (125mg/dl)	aspirin, IV steroids, cyclophosphamide, mycophenolate,	SNHL, visual field deficits, no residual central nervous system symptoms	therapeutic abortion	Wilf-Yarkoni 2020	

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Table 1. (Continued)

Case	SuS diagnosis before pregnancy	Age at diagnosis of SuS	Age at pregnancy	Gestational age or postpartum	Presenting symptoms	Audiometry	Ophtalmology	MRI	CSF	Treatment	Outcome	Pregnancy outcome	Reference	Prior symptoms and/or pregnancies
32	N		40	20	migraine, bradypsychia, disorientation and behavioral changes	SNHL	bilateral papillitis and ischemic retinal areas	T2 hyperintensities in the supratentorial white matter and corpus callosum with diffusion restriction		IVIG and oral prednisone; after pregnancy add-on of azathioprin	resolution of symptoms	healthy baby at 36-weeks GA after premature rupture of membranes and caesarean section	Ramos-Ruperto 2020	1 previous pregnancy without complications
32				6 months postpartum	bilateral scotomas		retinal infarctions			steroids (pulse), IVIG and cyclophosphamide	improvement		Ramos-Ruperto 2020	
33	N		37	puerperium	scotoma	SNHL	branch arterial retinal infarctions	T2 hyperintensities in supratentorial white matter, right internal capsule and splenium of the corpus callosum		steroids (pulse), oral prednisone and azathioprine	no relapses	healthy baby	Ramos-Ruperto 2020	2 previous pregancies; self-limited dysarthria and tinnitus during first pregnancy , as well as episodes of headache preceding the scotoma

AZA, azathioprin; BRAO, branch retinal artery occlusions; CSF, cerebrospinal fluid; CYC, cyclophosphamide; FA, fluorescein angiography; GA, gestational age; IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; OCB, oligoclonal bands; SNHL, *sensorineural hearing loss*; SuS, Susac syndrome; wbc, white blood cells.

pregnancy or in the postpartum period. In two patients, the first symptoms of SuS presented shortly after abortion (one spontaneous, one induced). Only two patients with SuS completed a pregnancy without relapses. In one patient, pregnancy was discovered when she was treated with cyclophosphamide (CYC) and the pregnancy was terminated for this reason. Pregnancy was terminated in six cases to allow treatment with potential foetotoxic drugs like CYC. Delivery of a healthy baby (at term or preterm) was described in 22 cases. One stillbirth and one spontaneous abortion were reported. Notably, six patients had one or more pregnancies, without symptoms of SuS, before the index pregnancy when SuS was diagnosed. Treatment during pregnancy consisted most frequently of steroids, anticoagulant or antiplatelet therapy, with add-on intravenous immunoglobulins (IVIG) in six cases and plasma exchange (PLEX) in two cases. One patient started CYC at 28 weeks gestational age due to ongoing relapses and she delivered a healthy baby.[30] Most patients improved on therapy, but residual cognitive, visual and/or hearing impairments were present in most patients. Complete recovery was rare. A few patients had a history of symptoms, compatible with SuS.

Pregnancy planning: general

Fertility

While no specific reports have been published on fertility in patients with SuS, this topic is of importance. Indeed, treatment with CYC may induce infertility in young female patients who have not yet completed their family. The risk depends on the patient's age at treatment and the cumulative dose.[38] Consulting a fertility specialist before the start of this treatment is recommended. As SuS is more frequent in females than in males, a role for hormones in pathophysiology may be suspected. A case of a SuS relapse after starting oestrogen replacement therapy, in a patient who had been in remission for 18 years, has been reported, suggesting the possibility of a role for hormones in triggering late relapse.[39] However, recently a female-to-male transgender patient developing SuS under treatment with testosterone was described, challenging the hypothesis of (female) sex hormones as important players.[40] Alternatively, this coincidence may not be associated with hormonal treatment at all, as men and women both can be affected. Whether oral contraceptive pills and hormonal treatments used during *in vitro* fertilisation (IVF) procedures may increase the risk of SuS or SuS relapse remains to be elucidated. A first case of SuS remaining in remission after a successful IVF procedure was published recently .[35] Usually patients with SuS are advised to change their systemic contraception to a local method because of the unknown impact of hormonal treatment,[41] but the evidence to support this strategy is scarce and is in part taken from the concept that hormonal treatments are considered prothrombogenic.

Genetics and heritability

To our knowledge, no cases of familial SuS have been published. No studies on (immuno)genetics have been reported to date. In a study with 14 patients, all but one SuS patient who was homozygous for HLA C*04, expressed HLA-C*06 and/or HLA-C*07. Comparing the peptide binding motifs of these HLA-C allotypes revealed that the binding motifs of HLA-C*06:02 and HLA-C*07:02 are almost identical.[5] SuS is considered to be a non-hereditary disease. However, as in other autoimmune diseases, such as multiple sclerosis (MS), genetic risk factors likely play a role in the development of the disease. This field is still open to research.

Disease activity monitoring

For patients who have a known diagnosis of SuS, regular clinical monitoring during pregnancy and the postpartum period is advisable, to detect disease relapse or recurrence at an early stage. Indeed, the reported cases demonstrate that there is a risk of disease onset and recurrence in these periods. During pregnancy, brain magnetic resonance imaging (MRI) is generally considered to be safe, especially when benefits outweigh potential risks. Gadolinium contrast is not administered during pregnancy, due to slightly increased risk of neonatal death. Moreover, T2 hyperintensities and diffusion weighted imaging, which can show the typical callosal lesions, may be a worthwhile alternative to gadolinium-enhanced MRI.[42] For patients who are diagnosed during pregnancy, a fluorescein angiogram may add important diagnostic information. However, fluorescein may

cross the placenta and enter the amniotic fluid. There are no teratogenic risks in animals. Safety information in humans is limited and therefore the decision to perform a fluorescein angiography should be made on a case-by-case basis and be performed only when the benefits outweigh the potential risks.[43]

Timing of pregnancy

SuS patients attempting pregnancy should preferably be free from disease activity and stable without therapy or stable on a treatment that is compatible with pregnancy. Advance pregnancy planning and counselling is therefore highly recommended in this patient group. It is generally accepted now that women with autoimmune diseases like systemic lupus erythematosus (SLE) and vasculitis may attempt pregnancy during quiescent periods of their disease, maintaining a compatible therapy during the preconception, pregnancy and postpartum periods.[44,45] In our opinion, the same advice may be applied to SuS patients. Attempting pregnancy when the disease is not (temporarily) in remission should be advised against, because of the risks to the mother when SuS flares up. Disease remission for a duration of at least 6 months seems prudent before attempting pregnancy. This advice is in accordance with recommendations for patients with SLE who wish to become pregnant.[44] However, disease remission for 6 months is no guarantee of no relapse during pregnancy, as disease recurrence has been described 23 years after initial symptoms, potentially elicited by pregnancy.[25] In conclusion, timing of a pregnancy should be a shared decision between patient and clinician, and patients should be informed of the risk of disease relapse during or after pregnancy.

Compatibility of commonly used treatments for SuS with pregnancy and breastfeeding

Recommendations on treatment of SuS have been published recently and are based on expert opinion.[8] There are no guidelines on treatment of SuS during pregnancy, where potential foetal toxicity of treatments needs to be taken into consideration. In the reported cases from patients with SuS during pregnancy, mainly steroids, IVIG and PLEX have been utilized during pregnancy, whereas cyclophosphamide and rituximab were kept for severe and refractory cases, after delivery (see Table 1). However, in one severe case, CYC was started in the 28th week of pregnancy because of ongoing relapses, without foetal toxicity.[30] It is important to note that all treatments described for SuS are off-label use.

Corticosteroids. Corticosteroids are used to treat disease flares, both intravenously in a high-dose pulse and orally in tapering schedules. Risk monitoring during pregnancy consists of following glycemia and blood pressure. Corticosteroids should be avoided in the first trimester, if possible, especially between 8th and 11th gestational week to reduce the slightly elevated risk of cleft lip and palate, but data are scarce.[46] One single pulse seems to be safe, while repeated or continued administration of corticosteroids may lead to growth retardation or preterm birth. Others state that prednisolone and methylprednisolone use is safe even in the first trimester.[47] Methylprednisolone and prednisolone should be preferred over dexamethasone, because penetration of the placental barrier is only 10%.

Intravenous immunoglobulins. It is important to assess the serostatus of the patient before starting IVIG, as administration of IVIG may lead to false positive serologic results. Indeed, serologic testing will detect endogenous IgG, produced by the patient, as well as administered IgG.[48] IVIG will cross the placenta. IVIG are used widely in the treatment of SuS: many case series and case reports describe amelioration of symptoms, and expert opinion recommends IVIG or subcutaneous IG (scIG). IVIG are safe in pregnancy and breastfeeding.[47,49]

Plasma exchange. PLEX seems to be safe in pregnancy and has been used as a rescue therapy in different neuroimmunological diseases, such as MS, antiphospholipid syndrome, thrombotic thrombocytopenic purpura, neuromyelitis optica spectrum disorders (NMOSD) or myasthenia gravis (MG).[50,51] In SuS, PLEX seems to be useful in acute episodes.[21] There are no reports of immunoadsorption in SuS.

Mycophenolate mofetil. Mycophenolate mofetil (MMF) is teratotoxic (pregnancy loss, congenital malformations) and should be avoided in pregnancy. Men and women should use effective contraceptives strictly during the treatment period, and

women additionally for at least another 6 weeks. No information is available on the excretion and effects of MMF in breast milk; expert recommendation is to avoid breastfeeding with MMF [United States Food and Drug Administration (FDA)].[47]

Azathioprin. Data on azathioprin (AZA) in other immunological diseases do not show any teratogenic effect, but there are hints of premature births and low birth weight. Whether this is due to the underlying disease, to the drug itself or other drugs used in combination, needs to be resolved. Cases of infants with bone marrow depression after maternal AZA use have been described. These side effects seem to be rare and should be weighed against potential relapses when discontinuing the drug if the mother is stable.[47,50] Thus, in treatment-naive pregnant women with SuS onset, AZA should not be the first line treatment. However, AZA can be continued during pregnancy after risk/benefit evaluation. Regular monitoring of leucocytes and thrombocytes is advisable. During lactation, AZA is probably safe, as drug levels in breastmilk remain very low, especially 4 h after intake.[52]

Methotrexate. Methotrexate (MTX) is contraindicated in pregnant women because of the teratogenic effects. It should be stopped at least 3 months before attempting conception.[47] Data on excretion in breastmilk are scarce and lactation should therefore be avoided during MTX use.[53,54]

Cyclophosphamide. CYC is contraindicated in pregnant women because of the teratogenic effects. However, there is some preliminary evidence in the field of cancer treatment that chemotherapy could be administered during the second and third trimester, with low risk of severe problems for the foetus.[47,55,56] In selected cases, treatment with CYC during pregnancy after the first trimester can be considered, in a centre that has experience with management of complicated pregnancies with a multidisciplinary team of at least a gynaecologist, a neurologist and a neonatologist. CYC is excreted in breastmilk, may suppress the infants bone marrow and should be avoided during lactation.[57,58]

Tumour necrosis factor alpha inhibitors. Tumour necrosis factor alpha (TNF-α) inhibitors are contraindicated in patients with demyelinating disease as these therapies may increase inflammation and induce relapses, underlining the importance of an optimal differential diagnosis. In patients with SuS, TNF-α inhibitors seem to be helpful in case reports and case series in patients with relapses with classic immunotherapies.[59] Based on sparse data from case series and case reports, TNF-α inhibitors do not appear to be associated with a high risk of teratogenicity, but a harmful effect cannot be ruled out definitively. In rheumatological diseases, TNF-α inhibitor use may be associated with a higher rate of preterm delivery, but this may be due to disease activity. TNF-αa inhibitor should be discontinued around the third trimester when transfer across the placenta is greatest.[47,60] The decision to use TNF-α inhibitors as an off-label medication in pregnant women with SuS should be reserved for very severe or life-threatening disease. Breastfeeding is compatible with TNF-α inhibitors.[61]

Rituximab. Information on rituximab (RTX) in pregnancy is based on case reports of women with immunological and malignant diseases. The monoclonal antibody can pass the blood–placenta barrier. The average half-life of RTX is 20–31 days. RTX seems to be associated with a higher risk of premature births, with consideration of the potential harmful effect of the underlying disease as a concurrent cause. B cells will be depleted in newborns; thus, measuring B lymphocytes in foetuses is recommended if RTX has been administered after the 20th week of pregnancy. In NMOSD, RTX administration is recommended close to the time of conception to have a long-term protective effect during pregnancy.[47,50] RTX is transferred to breast milk in minimal amounts.[62,63] Moreover, in breastmilk-fed infants from mothers treated with anti-CD20 therapies, no negative impact on health of the infants up to the age of 1 year was detected.[64] To summarise, careful evaluation of the risks and benefits of stopping or the continuation of RTX treatment is necessary. In patients with severe autoimmune disease, it is acceptable to attempt pregnancy closely after the last RTX dose and to consider redosing of RTX if relapses occur during pregnancy.[65]

Natalizumab. Natalizumab (NAT) is registered as treatment for relapsing remitting MS (RRMS). Its mechanism of action is interesting, because it inhibits lymphocyte adhesion and thus migration through the blood–brain barrier, by blocking

alpha4-integrin. In one case, NAT was reported to exacerbate SuS.[66] However, in an animal model and in four SuS patients, disease improvement was seen.[5] One advantage of NAT is that it has been used during pregnancy in RRMS patients and seems relatively safe in clinical practice. However, insufficient data are available to draw firm conclusions.[67–69] Another issue is the risk of progressive multifocal leukoencephalopathy in patients who are likely immunosuppressed by other treatments received prior or concomitantly. From MS, it is known that a rebound of disease activity may occur after cessation of treatment with NAT. When used only in patients with high disease activity, or when alternative treatment options are lacking, treatment with NAT might be continued under careful and frequent control and consideration of all the risks and benefits in pregnant women with RRMS.[64,69] The last dose should be administered before the 30–34th week. During lactation, current data for administration of NAT are limited, but reassuring.[63,67,69] In conclusion, the mechanism of action of NAT and clinical experience suggest that this agent may be of interest in SuS patients.

Calcineurin inhibitors. Cyclosporin A (CSA) and tacrolimus (TAC) are used in NMOSD, MG and SLE, and sometimes in SuS.[51,61,70–72] TAC and CSA should not be started, but can be continued relatively safe in pregnancy. However, strict drug level monitoring is required to limit toxicities. Metabolites of CSA and TAC pass the placental barrier. No major malformations have been reported with CSA or TAC. Premature birth and low birth weight have been reported in humans (FDA). Most data have been derived from patients receiving organ transplantation. Caution in the use of these therapies during pregnancy in SuS is therefore warranted. Limited data suggest that the excreted levels of TAC and CSA in breastmilk are low and unlikely to negatively affect the infant. TAC and CSA are considered probably safe during breastfeeding.[73–75] However, caution is warranted and monitoring of drug levels in the infants blood may be necessary, as even with low amounts of CSA excreted in breastmilk, infant levels may have therapeutic concentrations in the blood.[76]

Acetyl salicylic acid. High-dose acetyl salicylic acid (ASA) should be used with caution in pregnancy. Low dose ASA (81mg) preconception has not been associated with increased risk of major adverse events when used throughout pregnancy.[77] Epidemiologic studies describe increased risk of miscarriage, cardiac malformations, and gastroschisis under ASA in early pregnancy; the absolute risk of cardiovascular malformations increased from less than 1% to up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy (FDA). For secondary stroke prevention, low dose ASA during pregnancy is reasonable, and breastfeeding can be considered during intake of low dose ASA.[78] In most patients with SuS, ASA is added to reduce the risk of vessel occlusion based on expert opinions; however, evidence is lacking. Luminal occlusion in SuS is caused by hypertrophied and reactive endothelial cells.[79,80] Whether ASA effectively reduces endothelial inflammation in SuS remains to be proven.

Nimodipine. Nimodipine is a calcium antagonist that leads to vasodilatation. It is lipophilic and can pass the blood–brain barrier. It has been used in SuS in the past, but the immunopathogenesis does not support the use of nimodipine.

Discussion

We have summarised more than 30 cases of SuS, with description of disease course and treatment during pregnancy or postpartum period. Strikingly, approximately two out of three patients of these cases were diagnosed during pregnancy. One likely explanation is that there is a publication bias towards new diagnosed cases in pregnancy, while pregnancies in SuS patients who are in remission and have a normal course are not reported. A prospective, international registry for patients with SuS, containing specific pregnancy forms, could be a solution to solve this potential reporting bias. Patients who are in remission and have pregnancies without relapse or complications, as well as their treating physicians, should be encouraged to share their data and participate in these registries. Patient-driven or active patient-participation in these registries may help to collect the necessary data. Another potential explanation of SuS relapse during pregnancy is the role of hormones and changes in the immune system. It is well-known that the course of several autoimmune diseases changes during pregnancy. Th1-related diseases such as rheumatoid arthritis or MS tend to stabilise, while Th2-related diseases like SLE or vasculitis carry a risk of exacerbation during pregnancy.[45]

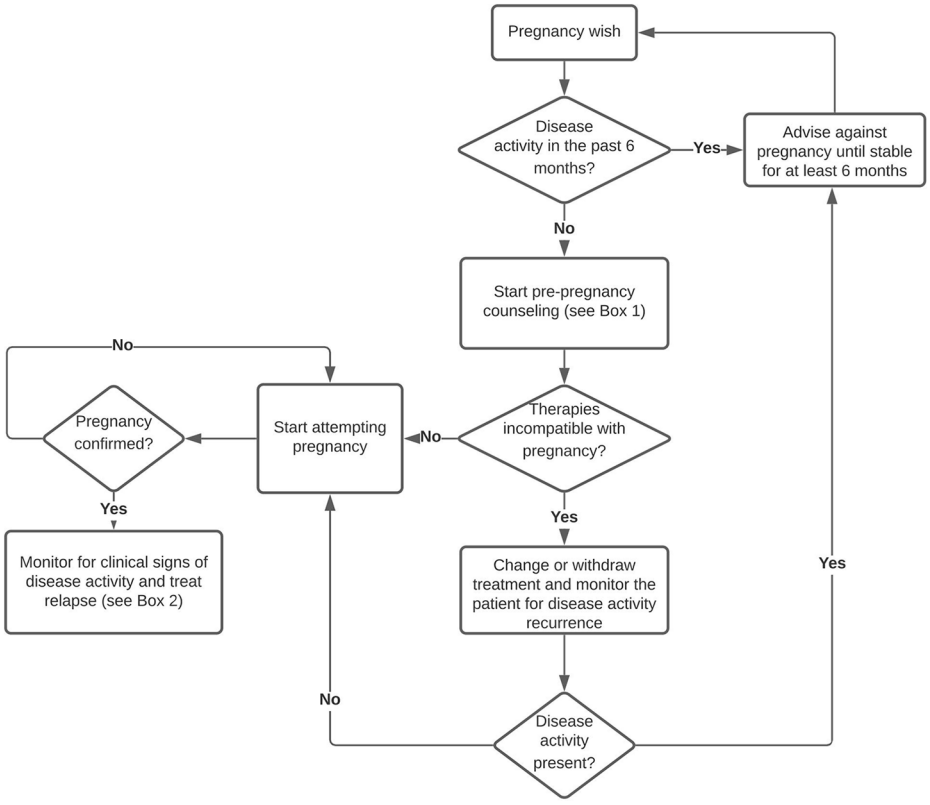

Figure 1. Management of pregnancy in SuS.
SuS, Susac syndrome.

Systematically studying the immunology of SuS before, during and after pregnancy may lead to better knowledge on pathophysiological mechanisms involved in disease relapse and remission.

Due to the rarity of this disease, there are no randomized controlled trials to guide treatment, and therapy is based on expert opinions and is, in part, based on knowledge of other immunological diseases. We propose a period of at least 6 months disease remission before attempting pregnancy (see Figure 1). This seems a reasonable approach in SuS and is in accordance with recommendations for patients with SLE.[44] In our opinion, and based on the risk profile of the drugs, for maintenance treatment during pregnancy, first choices are low dose oral (methyl)prednisolone and monthly IVIG. AZA, CSA and TAC may be considered as maintenance treatment during pregnancy, in patients who are known with SuS, but are not a first choice to start during pregnancy. MMF and MTX should be stopped before attempting conception and should not be started during pregnancy or lactation. RTX, with a last dose not too long before conception, may be a treatment option in patients who had severe disease and who wish to lower the risk of disease exacerbation during pregnancy as much as possible, in analogy with NMOSD management.[65] To treat SuS exacerbations during pregnancy and lactation, high-dose IV methylprednisolone can be considered, either alone or in combination with IVIG and/or PLEX. Adding ASA can be considered safe. In severe cases, RTX might be started and NAT might be continued during pregnancy, in analogy with treatment of severe SLE or RRMS. When treatment-refractory, very severe relapses occur, in the second or third trimester of pregnancy, after careful consideration, CYC can be regarded as a rescue therapy option, in analogy to other life-threatening autoimmune disease (see Box 1). During lactation, only small amounts of monoclonal antibodies are excreted into breastmilk. Therefore, TNF-α inhibitors, RTX and NAT may be relatively safe and considered to administer while breastfeeding.[62,64,69,81] Also, AZA, TAC and CSA may be safe during lactation.

Box 1. Recommendations on management of SuS patients before, during and after pregnancy.

PRE-PREGNANCY
- Information provision:
  Pregnancy in SuS should be considered as high-risk and it should be planned
  Discuss risk of relapse during pregnancy and post-partum and necessity of monitoring
  Discuss risks and benefits of immunosuppressive therapies
  Discuss limitations of current knowledge
  Refer or discuss case with expert in neuroimmunology
- Review disease status: stable for 6 months?
- Review treatment compatibility with pregnancy and adjust or withdraw treatments:
  Stop MMF, MTX, CYC
  Continue steroids in the lowest possible dose
  Continue IVIG
  Consider switch to IVIG alone or IVIG plus AZA or RTX

DURING PREGNANCY
Mother
- Include the patient in a registry if possible
- Monitor patients for occurence of clinical symptoms
- Perform brain MRI without gadolinium and ohtalmological examination without fluorescein in case of suspected relapse
- In case of relapse or first symptoms:
  First line treatment includes IV and oral (methyl)prednisolone, IVIG, PLEX and ASA
  Second line treatment includes RTX, NAT
  Rescue treatment is CYC
- In case of unexpected pregnancy and accidental exposure of the fetus to MMF, MTX or CYC: advise ultrasound and provide counselling about the risk of malformations

Fetus
- Perform structural ultrasound
- Monitor fetal growth

POST-PARTUM
Mother
- Perform baseline examinations with neurological examination, fluorescein angiogram, tone-audiometry and brain MRI in the month after delivery.
- Decision to breastfeed is dependent on personal risk-benefit evaluation

Baby
- Check B cell counts in the newborn in case of RTX use closely before conception or during pregnancy. Plan vaccinations accordingly.
- Evaluate the newborn for signs or symptoms potentially related to transferred antibodies and/or medication used during the pregnancy.

LACTATION
- IVIG is safe during lactation
- AZA, CSA, TAC, RTX, NAT or TNF-α inhibitors could be considered after risk/benefit evaluation
- (methyl)prednisolone (wait 1–4 h after dosing) or PLEX are safe in case of relapse

AZA, azathioprin; CSA, cyclosporin A; CYC, cyclophosphamide; IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; MTX, methotrexate; NAT, natalizumab; PLEX, plasma exchange; RTX, rituximab; TAC, tacrolimus; TNF-α, tumor necrosis factor alpha; SuS, Susac syndrome.

Finally, these pregnancies should be considered as high-risk pregnancies and follow up by or consultation with experts in the field of neuroimmunology is a prerequisite.

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