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Systemic sclerosis in pregnancy

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Abstract

Systemic sclerosis is a rare multisystem connective tissue disease. It predominantly affects women and poses a significant risk to mother and baby during pregnancy if not managed appropriately. The commonest manifestations are skin fibrosis and Raynaud's phenomenon. Subgroups of women have an increased risk of organ involvement, especially interstitial lung disease, pulmonary arterial hypertension and renal crises. Pregnancy increases the risk to the mother, especially those with established organ involvement, but also the development of new organ dysfunction; and risks to the fetus. Optimising these women prior to conception, along with careful management and surveillance during pregnancy, is vital for optimising pregnancy outcome. Women with scleroderma need to be managed in a specialised centre with coordinated care from the multi-disciplinary teams including physicians, obstetricians, anaesthetists, neonatologists and midwives. This review aims to describe the risks associated with systemic sclerosis and pregnancy, with management advice for physicians looking after pregnant women with this chronic condition.

Keywords

High-risk pregnancy, perinatal medicine, rheumatology, systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is a rare multisystem connective tissue disease (CTD) characterised by autoimmunity, fibrosis and vasculopathy. It has an incidence of 2–10 cases per million and is three to five times more common in women than men. This female predominance is even greater during the reproductive ages (15–50 years), where women have a 15-fold increase of being affected compared to men.[1] Women are categorised into limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) disease depending on the extent of skin involvement, with dcSSc involving skin above the elbows and knees including chest and abdomen.

Those most at risk of significant complications during pregnancy include those with dcSSc within five years of disease onset, those with anti-topoisomerase or anti-RNA polymerase III antibodies and those with organ involvement prior to conception. This includes previous scleroderma renal crisis (SRC), interstitial lung disease (ILD), with a forced vital capacity (FVC) less than 50% predicted, pulmonary arterial hypertension (PAH), active myositis including severe cardiomyopathy (ejection fraction less than 30%) and severe gastrointestinal (GI) involvement[2].

The majority of women with SSc report stable symptoms during pregnancy. Up to 20% report a deterioration in their symptoms during pregnancy, in particular among those with early stage disease,[3] with the most commonly reported symptoms being Raynaud's phenomenon (RP), digital ulceration (DU), arthralgia and skin thickening.[3] Internal organ progression may also occur specifically GI symptoms, arthritis, cardiac arrhythmias and renal crisis.[2,3] Pre-conception counselling should advise a delay in pregnancy if the woman has dcSSc and is within the first five years of disease onset.

Pre-pregnancy counselling

Contraception should be discussed with all women with SSc of childbearing age. Women with SSc who are considering pregnancy should be managed within a specialised multi-disciplinary team including specialists in SSc and obstetricians with experience in high-risk pregnancies. Pre-pregnancy counselling is vital, and should include organ assessment (including lung function and echocardiography) prior to conceiving, and the discussion of risks of pregnancy loss, morbidity and mortality. The effects of medications, in particular immunosuppressives, to both mother and fetus must be carefully evaluated (Table 1).

Fertility

Fertility is not reduced in women with SSc. However, a delay in conceiving may be experienced and may be due to early or active disease.[2]

SSc has a significant psychosocial impact on women due to the change in body and facial appearance. Body image dissatisfaction is reported to be higher than women with burns,[2] which has an impact in the formation of social and sexual relationships. Up to 37% of women suffer from vaginal dryness and dyspareunia, which in turn may prevent sexual intercourse.[1]

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Table 1. Monitoring and management of major complications associated with SSc.

Complication	Monitoring	Definitive tests	Treatment	Notes
Scleroderma renal crisis	Blood pressure monitoring, creatinine and urine dipstick	Blood film, renin, proteinuria, LDH, ADAMTS13 and PLGF	ACE inhibitor ± prostacyclin, iv glyceryl trinitrate	*DDx – pre-eclampsia* To continue ACE inhibitor
Interstitial lung disease	Clinical – cough and dyspnoea	CXR and HRCT	Modify DMARDs – azathioprine, tacrolimus, rituximab and treat reflux	Radiation dose low, so if clinically indicated, CT should be done
Pulmonary arterial hypertension/cardiac myositis	Oxygen saturations, regular echocardiography, lung function tests, 6-minute walk	Echocardiogram Cardiac MRI for right ventricular function	Epoprostenol, sildenafil and diuresis	Early termination/ delivery may need to be considered, ITU for haemodynamics monitoring
Skin	Clinical – skin tightening		Azathioprine or IVIg	
Raynaud's phenomenon/ digital ulceration	Clinical – new digital ulcers	Imaging – X-ray affected digit	Nifedipine, fluoxetine and Iloprost	Must exclude osteomyelitis
Gastrointestinal	History and clinical	Imaging OGD if concern re GAVE Hydrogen breath test	PPI, ranitidine, Gaviscon Metronidazole/ co-amoxiclav	Two-week course antibiotics for bacterial overgrowth
Myositis	Clinical, power assessment, muscle enzymes (CK, AST) and check thyroid	Electromyography	Azathioprine, IVIg and rituximab	

LDH: lactate dehydrogenase; ACE: angiotensin converting enzyme; PLGF: placental growth factor; CXR: chest X-ray; HRCT: high-resolution computerised tomography; DMARDs: disease modifying anti-rheumatic drugs; MRI: magnetic resonance imaging; IVIg: intravenous immunoglobulin; PPI: proton-pump inhibitor; OGD: oesophago-gastroduodenoscopy; GAVE: gastric antral vascular ectasia; CK: creatinine kinase; AST: aspartate aminotransferase; CT: computed tomography; DDx: differential diagnosis; ITU: intensive therapy unit.

Miscarriage

Most studies looking into miscarriage rates in SSc define miscarriage as a fetal loss before the 20th week of gestation. There are conflicting data on whether SSc increases miscarriage rates.[2] Increased risk of miscarriage has been reported among those late-stage dcSSc pregnant women (42% versus 13% in lcSSc and 13% in healthy controls).[4] However, more recently, Taraborelli et al. found early miscarriages (less than 10 weeks) in all subsets of SSc were comparable to the general obstetric population.[3]

The frequency of antiphospholipid (aPL) antibodies in SSc varies across studies. Some studies indicate that these antibodies are not clinically relevant, although there are reports of associations with catastrophic antiphospholipid syndrome and SSc sine SSc (visceral and immunological features of SSc without clinically detectable skin involvement). aPL antibodies can be found in up to 50% of SSc women with lower extremity digital ulcers.[5] These antibodies are also independently associated with pulmonary hypertension and macrovascular disease with increased mortality.[6]

Obstetric antiphospholipid syndrome (APS) is defined by the presence of aPL antibodies in association with a history of recurrent early miscarriages, late fetal loss or the suggestion of ischaemic placental insufficiency (intrauterine growth restriction (IUGR) or pre-eclampsia). Women with SSc should be screened for these antibodies prior to conception to ensure appropriate risk assessments are performed.

All women with known aPL antibodies or a history of obstetric APS should be offered low-dose aspirin prophylaxis from 12 weeks' gestation for pre-eclampsia prophylaxis. There is no evidence to suggest that the combination of SSc and aPL antibodies increases the risk of thrombosis in pregnancy. However, a history of late fetal loss should be treated with prophylactic low molecular weight heparin (LMWH) as the mechanism is thought to be related to thrombosis within the placenta. Women with a history of APS (aPL antibodies in association with thromboembolic disease) require prophylactic LMWH throughout pregnancy as well as specialist input from a haematologist and/or obstetric physician.

Maternal and fetal complications

It is well-documented in other autoimmune rheumatic diseases including systemic lupus erythematosus (SLE) that there are significant maternal and neonatal risks associated with pregnancy.[5] Similarly, recent studies suggest that SSc is associated with a higher risk of poor maternal and fetal outcomes and therefore needs to be managed carefully.

Fetal complications

Prematurity. Pre-term births are reported in 11%–40% of pregnancies in SSc, in particular in early dcSSc.[3,6,7] Risk factors include corticosteroid use, IUGR and very-low birth weight (LBW) (less than 1500 g). Folic acid usage is protective against pre-term birth in SSc, irrespective of medication use.[3] Despite prematurity, the overall rate of live births are 84% in lcSSc women and 77% in dcSSc, which is comparable to healthy controls (84%).[4]

Intrauterine growth restriction. IUGR and LBW babies are increased six-fold in pregnant women with SSc compared to healthy controls.[3] Additional fetal growth scans are therefore advised during pregnancy. Although pre-term birth and LBW are associated with increased steroid use, these results are confounded by the fact increased corticosteroid use is often associated with increased disease activity. This in itself increases the rates of all maternal–placental complications including pre-eclampsia.

Other considerations. Anti-Ro and/or anti-La autoantibodies are associated with a 2% risk of congenital heart block in the fetus, a risk

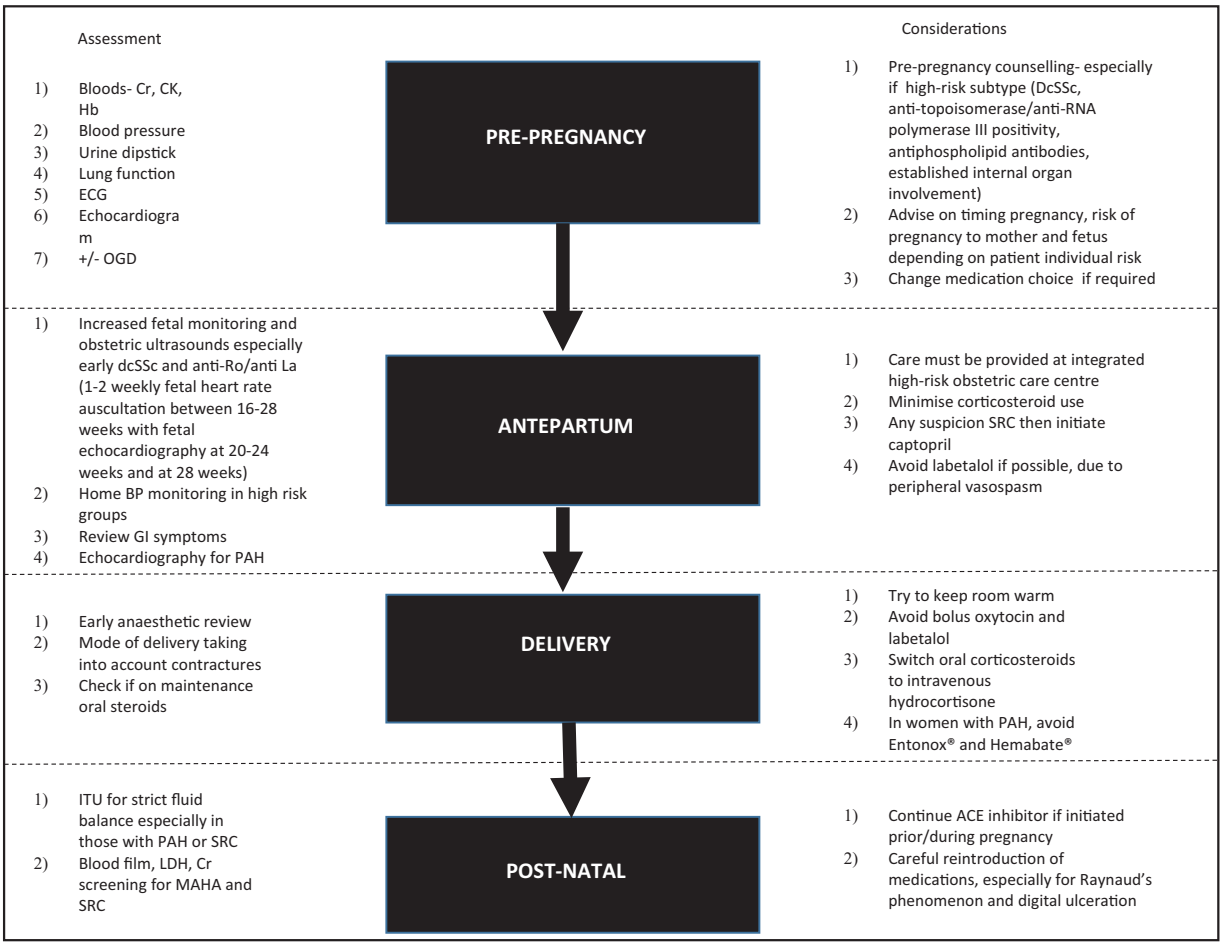

Figure 1. Figure depicting screening required and considerations for managing pregnant women with SSc during different stages of pregnancy. Cr: creatinine; CK: creatinine kinase; Hb: haemoglobin; OGD: oesophago-gastroduodenoscopy; BP: blood pressure; GI: gastrointestinal; LDH: lactate dehydrogenase; MAHA: microangiopathic haemolytic anaemia; SRC: scleroderma renal crisis; ACE: angiotensin converting enzyme; SSc: systemic sclerosis; ECG: electrocardiogram; PAH: pulmonary arterial hypertension; ITU: intensive therapy unit.

which increases with recurrent affected pregnancies (up to 10 times higher), and have a frequency of up to 37% and 4%, respectively, in SSc.[8] In pregnant women with mixed CTD and a history of a previous pregnancy affected by congenital heart block, hydroxychloroquine reduced the risk of recurrence.[9] It is unclear for those with SSc alone whether hydroxychloroquine reduces this risk. There is also a 5% risk of neonatal cutaneous lupus which can be disfiguring but is non-scarring. In the presence of these antibodies, regular fetal echocardiograms and fetal heart auscultation are advised from 16 weeks' gestation for early detection of congenital heart block (Figure 1).

Maternal complications

Scleroderma renal crisis. SRC is associated with significant mortality and morbidity, and angiotensin converting enzyme (ACE) inhibitors are the main therapeutic modality. As with other major organ complications in SSc, it occurs in the first few years of SSc, thus avoidance of pregnancy is advisable during this time. Pregnant women with anti-RNA polymerase III, anti-U3RNP antibodies and those on high-dose corticosteroids (more than 15 mg/day prednisolone or equivalent) are at greatest risk.[10] Pregnancy itself does not increase the risk of SRC,[6] and the rates in dcSSc are comparable to those outside of pregnancy. The incidence of SRC during pregnancy is reported around 2% with a peak between 16 and 28 weeks' gestation.[4]

SRC is often difficult to distinguish from pre-eclampsia or HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome. Rising blood pressure (BP; increase of 20 mmHg or more from baseline) with associated acute kidney injury (greater than 50% increase in serum creatinine from stable baseline) are essential criteria for the diagnosis, with evidence of haemolysis and microangiopathic haemolytic anaemia. Oliguria and pulmonary oedema can occur even with prompt treatment.[10] The BP of any pregnant woman at risk should be closely monitored throughout pregnancy.

Renal biopsy is the most accurate way to distinguish between SRC, pre-eclampsia and thrombotic thrombocytopaenic purpura (TTP). Renal biopsies in early pregnancy carry close to the same risk of complications as the general population, whereas late gestation biopsies carry increased risk of bleeding, and technical difficulties performing the procedure due to the gravid uterus. Therefore, it should only be performed in the third trimester if it will inform management. Supporting investigations to help differentiate these complications include ADAMTS13, placental growth factor (PLGF) and serum renin levels. ADAMTS13, a disintegrin and

metalloproteinase with a thrombospondin type 1 motif, member 13, is usually low or undetectable in TTP but normal in SRC and pre-eclampsia. The turn-around time of the ADAMTS13 result varies between institutions, and clinicians are advised to clarify this with their local laboratory, as treatment may need to be initiated prior to result availability. Raised renin levels are seen in SRC due to renal cortical ischaemia but are low or normal in pre-eclampsia. PLGF is used to distinguish pre-eclampsia from accelerated hypertension and proteinuria related to underlying renal disease. Uric acid and liver function are more frequently elevated in pre-eclampsia than SRC (Table 1).

ACE inhibitors should be started without delay if SRC is suspected and continued post-partum as renal function and BP do not recover immediately. Captopril is preferred due to the lowest incidence of fetal renal complications,[11] but other ACE inhibitors can also used. Although ACE inhibitors carry a risk to the fetus (oligohydramnios, intrauterine death, renal atresia and pulmonary hypoplasia when initiated beyond second trimester),[2] SRC is a life-threatening complication, and the risk to the mother outweighs any potential risk to the fetus.

BP management is crucial especially if there is any evidence of hypertensive encephalopathy or cardiac decompensation. If no organ complication has occurred, a 10% reduction in systolic BP per day is advisable.[10] Adjunct intravenous prostaglandin analogues (Iloprost), glycerol trinitrate, oral nifedipine and methyldopa may be required. Beta blockade, e.g. labetalol, is relatively contraindicated due to risk of peripheral vasospasm.

Pregnant women with a previous episode of SRC prior to pregnancy should have their BP optimised prior to conceiving (ideally 120/80 mmHg). Given the maternal risk from further deterioration in renal function and SRC, it is strongly encouraged to continue ACE inhibitors during pregnancy despite the risks to the fetus.[2] Some women are able to have a normal BP without an ACE inhibitor, whilst others will require other antihypertensives in conjunction with the ACE inhibitor to control their BP. However, due to the teratogenic risks of the ACE inhibitor, this discussion will need to be included in the pre-pregnancy counselling so the woman is aware of risks to the fetus.

Pulmonary arterial hypertension. PAH affects around 10% of women with SSc,[12] and is now the leading cause of death. Those most at risk include those with long-standing lcSSc, anticentromere, anti-topoisomerase or anti-Th/To antibodies, more than 10 telangiectasia and reduced capillary nail fold density. Women with SSc and PAH have a worse outcome than those with idiopathic PAH even without the added physiological stress of pregnancy.[13] Women with SSc routinely have an annual echocardiogram, lung function and pro B-type Natriuretic (pro-BNP) and urate. Decision on whether to investigate for PAH with a right heart catheter is decided based on the DETECT algorithm utilising these parameters, which allows for confirmation of the diagnosis[14] (http://www.detect-pah.com/home). Given the haemodynamic changes that occur during pregnancy, it would be recommended for all women with SSc to have had their routine annual surveillance of an echocardiogram and lung function tests prior to conceiving in case a right heart catheter is required.

PAH remains a significant pregnancy risk, with high maternal mortality (17%–33%) and neonatal mortality (11%–13%).[15,16] The risk of death or significant decompensation is predominantly during the peri-partum and immediate post-partum period (up to two months).[8,17] Pre-pregnancy counselling is vital in those diagnosed with PAH, highlighting the severe risks involved. With no meaningful data on clinical parameters in PAH where pregnancy is deemed safe, the current EULAR (European League against Rheumatism) recommendation is to avoid pregnancy for those with any evidence of PAH,[18] or offer termination if rapid deterioration is seen early in pregnancy.

Women with PAH wanting to get pregnant need to be cared for at a specialist pulmonary hypertension centre. They should have their pulmonary vasodilators maximised early to ensure stability of disease control, namely, the prostanoids and phosphodiesterase-5 inhibitors. Given both endothelin receptor antagonists and soluble guanylate cyclase stimulators are teratogenic drugs, it is recommended that they are stopped prior to conception or immediately thereafter. Soluble guanylate cyclase stimulators are associated with hypotension and bleeding, as well as teratogenic effects in animal models including cardiac ventricular septal defects.[19] Endothelin receptor antagonists were noted to cause significant cardiovascular malformations, severe craniofacial abnormalities and skull bone abnormalities in animal models.[20] Their use however, should not be entirely discounted later in pregnancy, as the risks to the mother may outweigh the fetal concerns outside the first trimester. Anticoagulation should be switched to low-molecular-weight heparin for the duration of pregnancy. Regular echocardiograms are required during pregnancy, monitoring right ventricular (RV) function. Pregnant women with severe PAH will require early elective delivery (sometimes earlier than 34 weeks' gestation) and an inpatient stay post-partum on the intensive care unit for meticulous fluid balance and monitoring of the RV filling pressure. Aggressive diuresis and ventilatory support (sometimes extra-corporeal membrane oxygenation (ECMO)) may be required[15] (Table 1).

Entonox® (50% nitrous oxide, 50% oxygen) and prostaglandin PGF2α (such as Hemabate®) should be avoided during delivery as an increase of circulating volume as little as 500 mL can cause decompensation.[15] General anaesthesia carries a four-fold increased risk of maternal mortality,[16] so should be reserved for an emergency.

RP and skin. Symptoms from RP and DU tend to improve during pregnancy (32% and 20%, respectively) with only 1% reporting deterioration in RP symptoms and 4% in DU.[3] Deterioration in symptoms is common post-partum. Improvement is attributed to the decrease in peripheral vascular resistance during pregnancy and an increase in cardiac output. Digital gangrene is often the result of other complications such as addition of beta-blockers or sepsis during pregnancy.[2]

Many pregnant women can stop their peripheral vasodilators during pregnancy but require reinitiation post-partum. This is especially important in those who have had previous DU. For those whose symptoms do not improve enough, it is appropriate to continue on nifedipine, fluoxetine and prostacyclin and sildenafil should be used with caution.[21]

The majority of pregnant women report stability in skin thickening during pregnancy, but post-partum up to 15% with both dcSSc and lcSSc will experience worsening of the skin score by a mean of 7.3.[3] Mild progression of skin disease during pregnancy would warrant initiation of hydroxychloroquine, whereas in cases of rapidly progressive skin disease and/or myositis, azathioprine will be required as immunosuppression, with the addition of intravenous immunoglobulin (IVIg) in extreme cases.[8]

Interstitial lung disease. ILD is common in SSc with up to 90%–100% of women having a degree of parenchymal lung involvement.[22] Many have asymptomatic disease detected on high-resolution computed tomography or pulmonary function tests. Clinically significant ILD commonly presents with progressive dyspnoea with or without a persistent dry cough.

Breathlessness is a common symptom of pregnancy and occurs in up to a third of women. Distinguishing physiological breathlessness from an underlying pathology can be challenging, given there is a significant increase in oxygen demand during pregnancy.

Majority of pregnant women with SSc report stable ILD during pregnancy;[23] however, based on limited studies, they have an increased risk of type 1 or type 2 respiratory failure.[24] Close monitoring of spirometry and oxygen saturations are important from the second trimester. Some women require supplemental oxygen or non-invasive ventilation to treat worsening respiratory failure. Pregnancy with FVC less than 50% of predicted or 1 L is associated with adverse pregnancy outcomes and potential pre-term delivery and is therefore often discouraged in these women. Women should be established on azathioprine or alternatively tacrolimus prior to pregnancy if required but may require extra corticosteroids if deterioration occurs.

GI symptoms. GI tract complications affect up to 80% of individuals with SSc.[25] Most have oesophageal involvement. Delayed gastric emptying, small intestinal, colonic and anorectal involvement may lead to significant symptoms including abdominal pain, vomiting, distension, diarrhoea, constipation and incontinence.

Pregnancy causes decreased peristalsis, delayed gastric emptying and prolonged small and large bowel transit times. Constipation, nausea and vomiting are common in pregnancy and SSc, whilst reflux symptoms can increase as pregnancy advances.

Upper GI symptoms worsen in up to 20% of SSc women during pregnancy. Those with reflux should be offered regular proton-pump inhibitors (omeprazole and lansoprazole) or H2 blockade (ranitidine) (Table 1). Gaviscon (aluminium hydroxide and magnesium carbonate suspension) can also help relieve reflux symptoms. Pro-kinetic antiemetics (domperidone or metoclopramide) can be used in addition to help reduce GI transit time.[3]

Overlap myositis. Muscle involvement in SSc includes idiopathic inflammatory myopathies (IIM) such as polymyositis (PM), dermatomyositis and rarely fibrosing myopathy, necrotising myopathy and sarcopenia. SSc-associated PM (SSc-PM) has a reported incidence of 5%–10%,[26] with associated autoantibodies including PM-Scl, anti-U3RNP and anti-Ku.[27] Cardiac and GI involvement convey the worst prognosis.

IIM in pregnancy is rare. In pregnant women with pre-existing SSc, myositis can predate the pregnancy with a risk of flare peripartum, especially in those who conceive with active disease. De novo presentations can occur during pregnancy and post-partum.[28] All pregnant women with SSc and pre-existing myositis should have inflammatory markers (C-reactive protein, creatinine kinase, pro-BNP and troponin) checked at each appointment. Erythrocyte sedimentation rate has limited use as it typically rises during pregnancy.

Symptoms of active myositis typically include weakness especially in the proximal muscles with or without worsening shortness of breath on exertion. A suspected flare of myositis warrants urgent repeat of the above investigations as well as tests for acute infections (including viruses such as influenza A&B, coxsackie, Epstein-Barr virus, cytomegalovirus, Varicella-zoster virus), vitamin D deficiency and hypothyroidism. Steroid-induced myopathy can mimic or trigger a flare. In de novo presentations, magnetic resonance imaging (MRI) and muscle biopsy for histological confirmation are the gold standard. All pregnant women with suspected cardiac involvement should have an electrocardiogram, echocardiogram and a cardiac MRI, taking into account the need for gadolinium given its relative contra-indication during pregnancy (Table 1).

Active myositis peri-partum has been associated with poor fetal outcomes.[29] Early diagnosis and prompt initiation of treatment with high-dose corticosteroids, azathioprine and IVIg are required. Resistant or aggressive disease may require rituximab or cyclophosphamide.[30] Pregnant women presenting acutely in cardiac failure secondary to myocarditis should be considered for ECMO, and will require MDT discussion regarding early delivery of the fetus.[31]

Medication

Pre-pregnancy counselling must take into account current medications required for pregnant women with SSc in particular those with active disease and risk to the fetus. Mycophenolate mofetil (MMF) is commonly used in SSc, but must be stopped at least six weeks prior to conception, whilst methotrexate has a wash-out period of three months with high-dose supplemental folic acid 5 mg a day. Azathioprine, tacrolimus and hydroxychloroquine can be continued throughout pregnancy. Whilst corticosteroids can be continued or even increased to maintain disease control, their use should be considered carefully especially those with disease duration less than five years, as their use is associated with an increased risk of SRC.[6] This increased risk is seen at a prednisolone dose of 15 mg and above (or equivalent). Corticosteroids also carry risks in pregnancy including gestational diabetes mellitus.[32] Although not routinely used in pregnancy, cyclophosphamide can be considered during the second and third trimester in those with life-threatening complications.[33,34] Rituximab can be administered in active disease in the first trimester[35] but beyond that, its use is associated with neonatal B-cell depletion means other agents are usually preferred. IVIg is safe to be initiated or continued during pregnancy if required. Monitoring for disease stability in the context of medication adjustments is critical during this period.

Special considerations

Solid organ transplant for SRC, ILD and cardiac myositis is increasingly being used in individuals with severe SSc. Immunosuppressives must be tailored to ensure optimal graft outcomes whilst minimising infant risk,[35] namely, calcineurin inhibitors and azathioprine. Pregnancy should ideally be delayed for at least a year of good health has passed following organ transplantation.

Preparing for delivery

Pre-term delivery often necessitates the need for high-dose corticosteroids to accelerate fetal lung maturity. These large doses carry the theoretical risk of precipitating SRC, although this has not been reported in the literature to date.[2] The woman's individual risk and gestational age of the fetus must be considered prior to administration.

Choice of mode of delivery should take into account mechanical restrictions from contractures and skin tightening in addition to the risk of poor wound healing and postoperative ileus. For those women with PAH, elective caesarean section may be preferential but should be considered following multi-disciplinary team advice, weighing the risks and benefits of each delivery modality.[1]

Early anaesthetic assessment is encouraged (Figure 1). Intubation can be challenging, given the increased aspiration frequency in SSc secondary to oesophageal dysmotility, as well as mechanical difficulties from microstomia and skin contractions. Regional anaesthesia is preferred and has the added benefit of peripheral vasodilatation to the lower extremities, decreasing any risk of peripheral ischaemia. Lower doses are usually required, as pregnant women with SSc may have prolonged motor and sensory blockade after delivery.[36] This is also preferred in the context of PAH although does not completely negate the risk of hypotension.

If pregnant women are already on corticosteroids (equivalent dose of 7.5 mg prednisolone or more for two weeks or more), this should be switched to intravenous hydrocortisone to ensure an adequate stress response is achieved. Ergometrine and bolus oxytocin should be avoided, especially in those with PAH, as can precipitate increased peripheral vascular resistance and hypotension. A slow infusion of

oxytocin or misoprostol are safe alternatives, which do not have effects on pulmonary or systemic vasculature.[36,37]

In the early post-partum period, careful monitoring of BP (including home monitoring) and renal function is imperative, as the woman remains at high risk of SRC,[4] as well as heart failure and cardiovascular collapse in pregnant women with PAH. This prolonged period of monitoring is required for at least 72 h but risk can remain elevated for the first two to four weeks post-partum. Medication stopped for pregnancy can be progressively reintroduced, but consideration must be made as to whether these are compatible with breast feeding (methotrexate and MMF remain contraindicated at this time).[21]

Conclusion

The emerging evidence from recent trials of biologics in early diffuse SSc and antifibrotics in progressive SSc-associated ILD will impact on the future management of pregnant women with SSc, in addition to reports of improved outcomes with combination therapeutics in PAH Critical to this is planned pregnancy in SSc with close engagement with expertise from across specialists within the multidisciplinary team to manage any potential maternal and fetal complications. It is envisaged that the results of IMPRESS 2 (International multicentric prospective case-control study on pregnancy in SSc) will provide further guidance on the management of pregnancy in SSc in particular the impact of pregnancy on disease activity and pregnancy outcomes in SSc.

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