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Pregnancy in systemic sclerosis

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ABSTRACT

This comprehensive review summarizes retrospective and prospective studies on pregnancy in systemic sclerosis in order to educate physicians on critical management issues. Fertility is normal in women with established systemic sclerosis. Their rates of spontaneous losses are comparable to the general population, except for patients with late diffuse systemic sclerosis and severe internal organ involvement who may have higher risks of abortion. Prematurity is clearly higher among systemic sclerosis women, similarly to other rheumatic diseases such as systemic lupus erythematosus and anti-phospholipid antibody syndrome. A placental vasculopathy has been observed in some women with systemic sclerosis. Overall, the disease generally remains stable in most pregnancies. Women with pulmonary hypertension should avoid pregnancy on account of the high maternal mortality risk. Management of systemic sclerosis patients before and during pregnancy includes evaluation of organ involvement and autoantibody analysis, preconceptional folic acid, and discontinuation of drugs with teratogenic potential (bosentan, mycophenolate mofetil, methotrexate, etc.). Management by high-risk pregnancy teams including neonatologists is very important to ensure the best outcomes.

Keywords: Systemic sclerosis, Scleroderma, Pregnancy, Prematurity, Renal crisis

The mean age at onset of systemic sclerosis (SSc) symptoms is in the early 40s, and women are now frequently delaying pregnancy. Moreover, attention has recently been drawn to so-called "early" SSc. The consequence is that pregnancy is no longer so rare in SSc women.

Sexuality and SSc

SSc has an important negative impact on sexuality due to fatigue, dyspareunia related to vaginal discomfort/tightness (1, 2), and the psychological implications of body appearance (3); these can be soothed using vaginal lubricants, keeping warm, and receiving psychological support. Sjogren's overlap and menopause may aggravate these problems. However, 60% of 101 SSc women interviewed in a study (4) were sexually active and only 17% of the others attributed their inactivity to the disease.

Fertility and SSc

Years ago some authors argued that SSc could interfere with conception and pregnancy (5). In 1992, Englert et al. (6) led a retrospective study on 204 women with SSc, 233 women with primary Raynaud's phenomenon, and 189 healthy women and reported that the women with SSc were more likely than the general population women to have a delay of more than 12 months in conception or of being infertile, but they were no different from the women with primary Raynaud's.

In contrast, Steen and Medsger (7) in 1999 surveyed 214 women with SSc, 167 women with rheumatoid arthritis (RA), and 105 healthy controls about their obstetric history. As in earlier studies, they noticed a statistically significant higher rate of nulliparity among women with an autoimmune disease (21% SSc, 23% RA, 12% controls; $p < 0.05$), but this difference disappeared after adjusting for factors such as the number of

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TABLE I - Studies on miscarriages after onset of systemic sclerosis

Author	Years	Design	Notes	No. of SSc pts	No. of pregnancies	Miscarriage rate	Other groups' miscarriage rates	Significance
Silman (13)	NA, ≤1988	Retrospective/ questionnaire	Only women under 35 years	115	NA	29%	GOP 17%	Yes (p=0.05)
Steen and Medsger (7)	1972–1986	Retrospective/ questionnaire		NA	89	15% of pregnancies	GOP 12%	No
							RA 13%	No
Steen (15)	1987–1996	Prospective		59	91	14% of pregnancies	GOP 13% of pregnancies	No
						19% of women	GOP 35% of women	No
Sampaio-Barros et al. (2)	1991–1998	Retrospective		NA	42	19% of pregnancies	NA	NA
IMPRESS Study (16)	2000–2011	Prospective	Only spontaneous abortions before 10 weeks were considered	99	109	4% of pregnancies	NA	NA

pts=patients; NA=not available; GOP=general obstetric population; RA=rheumatoid arthritis.
Miscarriage is defined as spontaneous abortion before the 22nd week of gestation (Ref. Lancet 2011). In the IMPRESS study, spontaneous abortions before 10 weeks of gestation were considered early abortions.

women who had never married, who were sexually inactive, or had chosen not to have children. Avoiding these biases, rates of infertility (2%–5%) and delays in conception of more than 1 year (12%–15%) were similar in the three groups. The overall successful pregnancy rates in patients with a prior period of infertility were also comparable in all three groups (around 40%).

Sampaio-Barros et al. (2) published retrospective data on 150 SSc women: 118 gave birth to 406 children and 42 of them after disease onset. The overall fertility rate (3.4) was similar to the general Brazilian obstetric population, with a significant difference between limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) forms (3.6 vs 3.1). The women who developed SSc before pregnancy had higher fertility rates than the normal population.

Two related issues are contraception and the possible side effects of treatment. As regards contraception, there are no specific concerns for women with SSc. Estrogens may be considered, particularly in women negative for anti-phospholipid antibodies and not smoking; intrauterine devices (IUDs) are allowed and barrier contraceptives can be used (8).

In fertile women with autoimmune diseases, cyclophosphamide is related to a higher rate of amenorrhea, nulliparity, and infertility; these adverse effects are dependent on the cumulative dosage and the woman's age and can be attenuated with gonadotropin-releasing hormone (9).

Effects of SSC on pregnancy

Abortions and miscarriages

According to the World Health Organization, miscarriage is defined as every loss before the 22nd week of gestation (10) and stillbirth a loss after that week, but it is also useful to distinguish between early abortions (up to 10 weeks) and later loss (10 weeks or more), also defined as fetal deaths in the anti-phospholipid literature (11)

Tab. I summarizes published data on abortions and miscarriages. In previous decades, only retrospective studies were available. Giordano et al. (12) observed 50 miscarriages in 299 pregnancies of 80 SSc patients; Silman and Black (13) noted that 29% of SSc patients had miscarriages before the age of 35 years, while the rate was significantly lower (17%) among healthy women. Englert et al. (6) too found higher miscarriage rates among women who subsequently developed SSc than in the general population and argued that these blighted pregnancies might result in transplacental transfer of cells, turning into a chronic graft-versus-host disease. However, a retrospective Spanish study (14) found no significant difference in miscarriage rates between 75 pregnancies of 28 women who later developed SSc and 61 pregnancies of 20 healthy women.

In a retrospective case-control study, Steen and Medsger (7) found a miscarriage rate among SSc women no different from that in the general population (9% vs 7.5%). In the same cohort, women were more likely to have miscarriages after disease onset than before (15% vs 8%).

The first fully prospective study on SSc pregnancy was published by Steen (15); the author followed 91 pregnancies in 59 patients. The frequency of miscarriages was significantly higher in the group with late diffuse disease (42% vs 13% for all the other groups); among the 7 women of this cohort who had miscarriages, 2 already had renal insufficiency and severe gastrointestinal malabsorption at conception; 20 had had 31 pregnancies before the study,

TABLE II - Pregnancy and maternal outcomes after onset of systemic sclerosis

Author	Years	Design	No. of SSc patients	No. of pregnancies/ deliveries	Renal crisis rate	Hypertension rate	Pre-eclampsia rate	PROM rate	Cesarean delivery rate
Steen and Medsger (7)	1972–1986	Retrospective/ questionnaire	NA	89/74	2%				
Steen (15)	1987–1996	Prospective	59	91/67	2%				
Sampaio-Barros et al. (2)	1991–1998	Retrospective	NA	42/34					
Chakravarty (17)	2002–2004	Retrospective cohort study	NA	NA/149		*23%*		*1%*	
IMPRESS Study (16)	2000–2011	Prospective	99	109/98	0%	2%	0%	6%	*52%*
Chen (18)	2001–2011	Retrospective cohort study	42	NA/53		8%			*64%*

No.=number; PROM=premature rupture of membranes; SSc=systemic sclerosis.
The italicized values represent statistically significant differences.

with 9 miscarriages and 3 neonatal deaths in these previous pregnancies.

The IMPRESS study (Italian Multicentric Study on Pregnancy in Systemic Sclerosis) recorded 109 pregnancies in 99 SSc patients; data were prospectively collected 1 year before conception, in each trimester of pregnancy and after delivery, and were retrospectively reviewed following a uniform protocol (16). This cohort was compared with a general obstetric population (GOP) comprising all 3939 deliveries recorded in 2009 in one participating center.

Among SSc women, early abortions (before10 weeks) occurred in 4%, fetal deaths (at or after 10 weeks) in 2%, and voluntary/therapeutic abortions in 4%; in the GOP, early abortions and fetal deaths had similar rates (5% and 3%). From unpublished data, the authors noticed that previous pregnancies—not followed as high-risk conditions—had had worse rates: miscarriages happened in 25% of cases and fetal deaths in 5% (5).

In summary, the risk of spontaneous losses in SSc women followed as high-risk pregnancy can be comparable to the general healthy population, though late diffuse SSc might involve a higher risk.

Obstetric complications

All kinds of major obstetric complications (e.g. pre-eclampsia, abruptio placentae, premature rupture of membranes, placenta praevia, excessive bleeding) have been reported in SSc patients (see Tab. II). Chakravarty et al. (17) used an administrative US discharge database for a population-based study in 504 hospital admissions of SSc women in maternity wards and noticed an increased risk of hypertensive disorders including pre-eclampsia. Chen et al. (18) too published a population-based cohort study, recording all live births or stillbirths (miscarriages before 20 weeks of gestation were not considered) in New South Wales from 2001 to 2011, with focus on 53 deliveries in 42 SSc patients; this study did not find any increase in the rates of pre-eclampsia, but there was a high percentage of cesarean deliveries (34 cases, 64% of SSc pregnancies compared with 28% in the GOP). The IMPRESS study recorded 51 cesarean sections among 98 deliveries (52%), a significantly higher rate than in the GOP (31%): 20 cesarean sections were done as an emergency (9 for obstetrical reasons and 11 for fetal distress) and 31 were elective (14 because of concern about maternal disease although there was no real deterioration).

Premature birth

According to the World Health Organization, prematurity is defined as any birth before completing the 37th week of gestation. In the GOP, preterm rates differ in different decades and world zones, but in developed countries, they are currently about 5% (19). Data in SSc cohorts are summarized in Tab. III.

The first studies showed no difference between SSc women and healthy controls (4), but Steen and Medsger (7) retrospectively noticed that the frequency of premature births was higher in autoimmune diseases (both RA and SSc), and among SSc patients, rates were even higher when pregnancy occurred before the clinical onset of disease. Among premature births, one fetal death was the only major complication.

Confirmation of these findings came from Steen's (15) prospective study: preterm birth occurred in 29% of SSc pregnancies versus 5% of historical healthy controls, and this rate rose to 65% in women with early-diffuse SSc. Despite a tendency to premature births and the need for prolonged hospital stays for many babies, there was just one fetal death at 25 gestation weeks and the overall success rate was comparable to controls (84% in lcSSc, 77% in dcSSc, and 84% in controls).

Also, in the IMPRESS study (16), preterm and severe preterm (before 34 weeks) deliveries were more frequent in SSc patients than the GOP (25% vs 12% and 10% vs 5%, respectively). Comparing preterm deliveries in SSc women with those who

TABLE III - Pregnancy and neonatal outcomes after onset of systemic sclerosis

Author	IUGR		Preterm birth		SGA		Neonatal morbidity	
	Definition	Rate	Definition	Rate	Definition	Rate	Definition	Rate
Steen and Medsger (7)			<38 weeks	15%	Full term weighing <2.5 kg	11%	Neonatal death	5%
Steen (15)			<38 weeks	*25%*	Full term weighing <2.5 kg	0%	Perinatal death	1%
Sampaio-Barros et al. (2)							Perinatal death	0%
Chakravarty (17)	<10th percentile	5%						
IMPRESS Study (16)	<5th percentile	6%	<37 weeks/<34 weeks	*25%/10%*	Birth weight <10th percentile for GA	*14%*	Fetal death >10 weeks	2%
Chen (18)			<37 weeks	*13%*	Birth weight <10th percentile for GA	*5.7%*	Life-threatening conditions	23%

IUGR = intra-uterine growth restriction; SGA = small for gestational age; GA = gestational age.
The italicized values represent statistically significant differences.
Neonatal death: <28 days of age; perinatal death: >20 weeks of gestation or <28 days of age.

delivered after 37 weeks, univariate analysis showed a higher rate of use of corticosteroids (40% vs 21%) and lower folic acid intake (36% vs 68%) in women who delivered preterm infants, while anti-Scl70 antibodies were less prevalent. In multivariable analysis too, folic acid and anti-Scl70 antibodies seemed protective (odds ratio (OR) 0.30 and 0.26, respectively), while corticosteroids were associated with preterm deliveries (OR 3.63).

Fetal growth restriction and small-for-gestational-age infants

Fetal growth restriction (FGR), also known as intra-uterine growth restriction (IUGR), is defined as ultrasonographic findings of fetal abdominal circumference below the 5th percentile for gestational age. Small-for-gestational-age (SGA) infants are newborns whose birth weight is below the 10th percentile for gestational age. Both of these are signs of fetal chronic suffering and risk factors for significant morbidity and mortality (Tab. III). Chakravarty et al. (17) found an increased risk of FGR (OR: 3.74, 95% confidence interval (CI): 1.51–9.28), and the IMPRESS study too (16) confirmed that FGR was more frequent in SSc women than in the GOP (6% vs 1%). In different case-control studies, rates of SGA were high among patients with primary Raynaud's phenomenon (6) and SSc but not RA (7). The IMPRESS study, however, did not record any increase in the SGA rate compared to the GOP, but very-low-birth-weight (VLBW infants, less than 1500 g) were significantly more frequent among SSc women (5% vs 1%), probably in relation to the high rate of preterm deliveries (16). Six newborns were admitted to the intensive care unit; one severely premature infant (27.4 weeks of gestation) died of multi-organ failure.

These findings might be epiphenomena of SSc vasculopathy affecting the placenta: placentas from SSc pregnancies had normal weight for gestational age (5), but histopathologic studies from a limited number of cases (20, 21) showed decidual vascular abnormalities, placental mesenchymal dysplasia, and chronic villi infarcts. An immunohistochemical analysis (21) found enhanced expression of vascular endothelial growth factor (VEGF) and its type-2 receptor (VEGFR-2) in vessel walls. All these findings are similar to those seen in pregnancies complicated by pregnancy-induced hypertension and are associated with a poor neonatal outcome. Malnutrition may occur in SSc patients (22) both because of lower food intake (secondary to mood disorders, reduced oral aperture size, xerostomia, dysphagia, gastric dysmotility) and malabsorption (due to small intestine bacterial overgrowth). This may increase the risk of FGR (23)

Effects of pregnancy on SSC

Evaluation of the possible effects of pregnancy on SSc course is challenging, considering that many symptoms are common in normal and SSC pregnancies (edema, arthralgias, gastrointestinal reflux, and shortness of breath); see Tab. IV for a summary. First small studies described cases of poor maternal outcomes due to renal crisis, but larger studies by Steen and the IMPRESS centers (7, 15, 16) found no significant changes in disease status during pregnancy. In the prospective study by Steen (15), 61% of pregnant women were stable, while the same proportions of others—20%—experienced worsening or improvements. There were no differences in 10-year survival between SSc women with or without a pregnancy.

Renal crisis

Recent studies of SSc pregnancies have found a lower incidence of renal crisis than that reported in the early literature. In the prospective study by Steen (15), among 91 pregnancies,

TABLE IV - Changes in SSc during pregnancy

Involvement	Changes in pregnancy
Overall	Generally disease stability
Renal	No differences in renal crisis rates
Cardiopulmonary	No significant differences
Cutaneous	Skin thickening worsening in a minority of women
Raynaud's phenomenon	Temporary improvement
Gastrointestinal	Worsening of reflux
Joints	Worsening of arthralgia

SSc=systemic sclerosis.

2 developed renal crises: one required an elective abortion at 20 weeks with the aim of controlling the crisis (but still needed dialysis); the other underwent dialysis for a short time and was successfully treated with angiotensin-converting enzyme (ACE)-inhibitors. Both had early-diffuse SSc.

In the IMPRESS study (16) there were no renal crises during the 109 pregnancies, but a 30-year-old woman with an anti-topoisomerase-positive dcSSc since the age of 24 years suffered a renal crisis 1 month after delivering an SGA infant at 37 weeks; she started high-dose ACE-inhibitors and bosentan and underwent dialysis for 4 years, culminating in stage IV chronic kidney failure.

Nevertheless, renal crisis remains the most serious complication of SSc and can be confused with pre-eclampsia because of the similar findings of hypertension and proteinuria. Some blood tests can help make a differential diagnosis: uric acid and transaminase elevations are more frequent in pre-eclampsia, while progressive daily increases in serum creatinine and microangiopathic hemolytic anemia are typical of renal crisis; plasma renin too is elevated in renal crisis due to renocortical ischemia (24). Renal biopsy can be helpful but it is not recommended during pregnancy on account of the high risk of complications then (25). New and specific biomarkers for early pre-eclampsia have been proposed, like the ratio of soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) (26), but their specificity remains to be evaluated in SSc pregnancies.

The milestone for renal crisis treatment was the introduction of ACE-inhibitors, which dramatically changed the outcome (27); they must be used in case of renal crisis even in pregnant patients, in spite of their teratogenic potential (28). There is no evidence that interrupting the pregnancy will reverse a renal crisis (5).

Pulmonary arterial hypertension

PAH affects around 10% of SSc patients and generally occurs in anti-centromere-positive, long-standing lcSSc (29), not usually involving fertile women, though it can also occur in younger patients, for example, with anti-U1 ribonucleoprotein (RNP) (30). PAH is a very threatening condition during pregnancy because of the physiological reduction in vascular resistance to accommodate the increased blood volume and cardiac output, and this can cause severe hemodynamic complications, especially in early post-partum. The maternal death rate in women with PAH is still around 17%–50% (31), in most cases due to acute cardiovascular collapse at delivery or during the subsequent 2 weeks. A prospective multi-center study (32) showed that this risk has remained substantial even in recent years and pregnancy must be discouraged in a patient with true PAH.

In the IMPRESS study (16), no patients had PAH, but an lcSSc African patient, anti-topoisomerase and lupus anticoagulant-positive, with systemic arterial hypertension and severe baseline pulmonary involvement (forced vital capacity (FVC) 37%, diffusing capacity for carbon monoxide/alveolar volume (DLCO/VA) 23% of predicted) developed pulmonary hypertension 9 months after a physiological pregnancy.

Cardiopulmonary diseases

SSc pregnant women do not seem to have worse cardiopulmonary outcomes than other pregnant women with similar cardiovascular status. Cardiovascular stress during pregnancy can unmask subclinical myocardial damage, especially with the usual treatment of preterm labor with beta-agonists. In the IMPRESS study (16), an anti-topoisomerase-positive short-standing (18 months) SSc patient developed severe myocarditis 6 months after a preterm delivery.

Apart from shortness of breath—quite common in GOP due to increased basal oxygen consumption and alveolar ventilation—there is no evidence of worsening of pulmonary fibrosis. In the IMPRESS study, 10% of women (two with lung basal involvement) reported shortness of breath during pregnancy, but with no organic pulmonary progression.

Skin and musculoskeletal diseases

Many patients report that their Raynaud's phenomenon and digital ulcers improve during the second or third trimester of pregnancy and then get worse again after delivery—for instance, in 32% and 22% of patients enrolled in the IMPRESS

TABLE V - Proposed pregnancy and post-pregnancy biomarkers/studies/assessments

Pre-pregnancy	During pregnancy	Post-partum
Assessment of risk according to autoantibody profile (including anti-phospholipid antibodies), cutaneous subtype, and organ involvement (including echocardiogram and pulmonary function tests). Higher risk in early-diffuse SSc and in women anti-topoisomerase or anti-RNA polymerase III or anti-phospholipid antibody positive Pregnancy is contraindicated in women with pulmonary arterial hypertension. Patients with prior renal crisis who require ACE-inhibitors may need to avoid pregnancy Discontinue potentially teratogenic drugs before conception (see Table 6) Start folic acid	Frequent blood pressure monitoring with aggressive treatment of hypertension Management by high-risk pregnancy teams including rheumatologist, obstetrician and neonatologist Blood tests are recommended at least monthly, including blood cell count, renal function, and liver tests. Periodic assessments of fetal growth and Doppler velocimetry of uterine and/or umbilical arteries should be considered	Blood pressure monitoring Rheumatological assessment post-partum and at least 1month after delivery Renal function monitoring

SSc=systemic sclerosis; ACE=angiotensin converting enzyme.

study (16). A possible explanation of these temporary modifications might be the increase in peripheral blood flow due to reduced systemic vascular resistance, typical of the hemodynamic changes during pregnancy. Only a few cases of acute gangrenous changes in late pregnancy were reported by Steen and Medsger (7) in patients who used beta-blockers or had problems like complicated deliveries and/or sepsis.

In Steen's (15) prospective study, 7 out of 59 women reported worsening of skin thickening after delivery; they all had dcSSc, but there were also some possible biases like discontinuation of D-penicillamine therapy prior to the pregnancy. In the IMPRESS study, the modified Rodnan Skin Score (mRSS) significantly worsened after pregnancy in 15% of the women.

As musculoskeletal complaints (for instance, cramps, arthralgia, and back pain) are common in all pregnant women, it is hard to establish whether their incidence is different in pregnant SSc; the IMPRESS study found that arthritis and joint contractures remained stable in 91% and 98% of patients, respectively.

Gastrointestinal diseases

Similar considerations hold for other typical complaints of pregnancy like constipation and esophageal reflux; this latter tends to be particularly evident in the second and third trimesters due to physiological inhibition of the muscle tone of the lower esophagus. In the IMPRESS study (16) pyrosis worsened in 19% of cases, vomiting in 11%, and diarrhea/constipation in 9%.

Developing SSc during pregnancy

There are few case reports describing new-onset SSc during pregnancy—only 5 of the 59 women in Steen's (15) prospective study—so it is not possible to assess whether SSc develops more frequently in pregnancy.

Pregnancy management

Counselling and multidisciplinary management is mandatory (rheumatologist, obstetrician and gynecologist experienced in pregnancies at risk, and neonatologist). Pregnancy planning including the possible use of contraceptives should be considered in order to assess organ damage and propose the best pharmacological timing and therapy (see the following sections and Tab. V).

Counselling

Women with cutaneous diffuse scleroderma and disease onset less than 4 years or positivity for anti-topoisomerase or RNA polymerase III antibodies have a greater risk of more aggressive disease than patients with long-standing disease and anti-centromere antibodies. Women with diffuse SSc of less than 3–4 years duration may be at higher risk of progression during pregnancy or after delivery, so postponing pregnancy or close follow-up should be considered. Nevertheless, no definite differences in pregnancy outcomes have been found between lcSSc and dcSSc patients.

Every SSc pregnant woman should be considered at high risk of premature infants and disease-related problems and should be closely followed by a high-risk pregnancy team including the rheumatologist, obstetrician, and neonatologist. In particular, blood pressure monitoring and periodic assessments of fetal growth and Doppler velocimetry of uterine and/or umbilical arteries should be considered.

In case of severe organ impairment (for instance, PAH, severe restrictive lung disease, renal failure, or cardiomyopathy), the decision to avoid or terminate the pregnancy should be considered. Patients with prior renal crisis who require ACE-inhibitors may also need to avoid pregnancy.

TABLE VI - Drugs commonly used in SSc and their effects in pregnancy and lactation

Drug	Pre-conception	Pregnancy—first trimester	Pregnancy–second and third trimesters	Lactation
Mycophenolate mofetil	Stop at least 3 months before conception	Teratogenic potential	Teratogenic potential	Not recommended
Methotrexate	Stop at least 3 months before conception	Teratogenic potential	Teratogenic potential	Not recommended
Bosentan	Stop at least 3 months before conception. Interference with oral estroprogestinics	Teratogenic potential	Teratogenic potential	Not recommended
Macitentan	Stop at least 3 months before conception	Teratogenic potential	Teratogenic potential	Not recommended
ACE-inhibitors	Stop before conception	Teratogenic potential	Teratogenic potential (but they must be used in case of renal crisis). The risk of renal atresia, pulmonary hypoplasia, or anhydramnios is worse in the second half of pregnancy	No contraindications
Nifedipine	No contraindications	No contraindications	No contraindications	Not recommended
Proton pump inhibitors and histamine blockers	No contraindications	No contraindications	No contraindications	No contraindications
Corticosteroids	To avoid/lowest dose possible	Avoid/lowest dose possible	Avoid/lowest dose possible	Lowest dose possible
Low-dose aspirin	No contraindications	No contraindications (it may reduce pre-eclampsia risk in high-risk pregnancies)	No contraindications	No contraindications
Folic acid	Recommended	Recommended	Recommended	No contraindications
Hydroxychloroquine	No contraindications	No contraindications	No contraindications	No contraindications

SSc=systemic sclerosis; ACE=angiotensin converting enzyme.
In 2015, the United States Food and Drug Administration (FDA) replaced the former pregnancy risk letter categories (*see below*) on prescription and biological drug labeling *with new information to make them more meaningful* to both patients and healthcare providers. The FDA received comments that the old five-letter system left patients and providers ill-informed and resulted in false assumptions about the actual meaning of the letters. Risk categories were as follows: A, no risk in controlled clinical studies in humans; B, human data reassuring or when absent, animal studies show no risk; C, human data are lacking and animal studies show risk or are not done; D, positive evidence of risk, benefit may outweigh; X, contraindicated during pregnancy.
According to the old FDA classification for drugs in pregnancies, mycophenolate was classified into category C, methotrexate category X, endothelin inhibitors category X, ACE-inhibitors category D, nifedipine category C, omeprazole category C, ranitidine category B, prednisone category B, aspirin category C, and hydroxychloroquine category C.

Heart block and anti-phospholipid antibody screening

Pregnant SSc women should be tested for anti-Ro/SSA antibodies: they are present in 12%–37% of SSc patients and are associated with the development of fetal heart block. The risk of congenital complete heart block is 1%–2% in anti-Ro/SSA-positive women, and echocardiograms and obstetric sonograms should be scheduled every 2 weeks from the 16th week of gestation to detect early abnormalities in the fetus at risk (33).

Anti-phospholipid antibodies (LAC, anticardiolipin, and anti-beta2glycoprotein I) may be present in 3%–13% of SSc women (16). Any woman with a rheumatic autoimmune condition who wishes to become pregnant should be tested for these antibodies; in case of positivity, low-dose aspirin plus heparin is generally proposed (34).

Drugs

Recently, a European League Against Rheumatism (EULAR) commission wrote a consensus statement on the use of antirheumatic drugs during pregnancy and lactation (35). Tab. VI describes drugs commonly used in SSc and their effects on pregnancy and lactation. Drugs with teratogenic potential like mycophenolate, methotrexate, or bosentan must be discontinued, preferably at least 3 months before conception; women in therapy with bosentan need to be particularly cautious because it interferes with oral contraceptives. Macitentan too has teratogenic potential, so PAH patients should not plan a pregnancy in any case. Despite their teratogenic potential (36), ACE-inhibitors must be used to deal with renal crisis. Calcium channel blockers can be used with caution, but usually are not necessary

because of the peripheral vascular improvement during pregnancy. Proton pump inhibitors (37) and histamine blockers are safe and can be used for gastrointestinal problems. Low-dose aspirin is allowed and is thought to reduce the risk of pre-eclampsia in women at risk (38). Corticosteroids may increase the risk of prematurity and should be avoided if possible (39), though the disease itself may facilitate prematurity; if used, low doses are definitely preferable (5). Folic acid must be started before conception to limit the risk of neural tube defects (40).

Management of renal crisis

As we mentioned earlier, the introduction of ACE-inhibitors dramatically shifted the poor prognosis of scleroderma renal crisis. The use of these drugs during pregnancy, however, involves a significant risk of malformations like renal atresia, pulmonary hypoplasia, or anhydramnios, and in contrast to other teratogenic medications, this risk is worse in the second half of pregnancy. It is therefore essential to distinguish renal crisis from pre-eclampsia (see section "Renal crisis"). Monitoring blood pressure is recommended, particularly in patients with recent-onset dcSSc. In case of renal crisis, therapy must be started as soon as possible, even when cesarean section is planned and maintained indefinitely. This is a strong limitation for women desiring a pregnancy after renal crisis, because replacing ACE-inhibitors with other anti-hypertensive medication is harmful for both mother and fetus if pressure control is incomplete (15).

Delivery and anesthesia

Diffuse skin thickening and secondary tissue contractures can hinder delivery and impair venous access. Intubation can be difficult due to microstomia while esophageal dysmotility and sphincter incompetence can lead to aspiration. Particular care is advisable for warming the delivery room and body surface. Regional anesthesia, especially epidural block, is recommended because it provides peripheral vasodilation and increases skin perfusion of the extremities; low doses of anesthetics may be used because SSc patients usually show prolonged motor and sensory blockade after delivery (41).

Post-partum follow-up

After delivery, it is important to monitor disease recrudescence, particularly worsening of skin lesions, reintroducing any drug treatments that may have been interrupted during pregnancy and assessing possible rare contraindications during breastfeeding. Close follow-up should continue for women with diffuse or recent-onset disease, especially if anti-topoisomerase positive.

Future prospects

Some important questions remain in SSc pregnancies. What is the role of placental SSc vasculopathy? Are complications of SSc more frequent during pregnancy than in the non-pregnant state? What is the current incidence of renal crisis, severe cardiac involvement, and pulmonary hypertension in scleroderma patients, pregnant or non-pregnant? Is folic acid protective against prematurity? What is the impact of prematurity on the child's development?

These questions might be answered by the ongoing IMPRESS 2 study (International Multicentric Study on Pregnancy in Systemic Sclerosis), a prospective controlled observational study, EUSTAR endorsed, partially funded by three patients' associations: GILS (Gruppo Italiano Lotta alla Sclerodermia), Gruppo LES Italia, ALOMAR (Associazione Lombarda Malati Reumatici) and by FIRA (Fondazione Italiana per la Ricerca sulla Artrite), enrolling prospective pregnancies in SSc women and comparing them to matched non-pregnant SSc women and healthy pregnant women. At the time of writing, 97 pregnant SSc women, 140 non-pregnant SSc women, and 200 healthy pregnant women had been enrolled. Data analysis will start in 2018.

Disclosures

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