Original Article

Outcome of Pregnancy in Systemic Sclerosis

Lingling Salang MD[1], Pranorm Buppasiri MD[1], Chingching Foocharoen MD[2]

[1] Department of Obstetrics-Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[2] Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Objective: A few studies have been published on the outcome of pregnancy among patients with systemic sclerosis [SSc] but to our knowledge none among Thai patients with SSc. Our objective was to determine the pregnancy outcome among Thai patients with SSc.

Materials and Methods: A 11-year retrospective study (between 2007 and 2017) was conducted at Srinagarind Hospital, Khon Kaen University. All pregnant women with SSc were enrolled to evaluate their pregnancy outcomes.

Results: Seven pregnancies from 5 women with SSc were reviewed. The pregnant women were between 23 and 37 years. Four of the 5 had the limited cutaneous SSc subset and two had overlap with other connective tissue diseases. Only 1 patient had pulmonary fibrosis before being pregnant but she continued the pregnancy without any worsening of the disease. Four of seven SSc pregnant participants required pregnancy termination for uncontrolled autoimmune hemolytic anemia, eclampsia with hemolytic elevated liver enzyme and low platelet [HELLP], fetal distress, and premature rupture of membrane, respectively. The pre-term delivery occurred in 2 pregnant SSc patients and the maternal and fetal outcomes were normal.

Conclusion: The number of pregnant SSc patients in the 11-year historical review was limited. Most of the patients had an uncomplicated pregnancy but the respective maternal and fetal outcome in those with SSc overlap with other connective tissue disease trended to be worse than in pure SSc. Family planning is suggested for all reproductive age SSc patients.

Keywords: Scleroderma, Systemic sclerosis, Pregnancy, Outcomes, Intrauterine growth retardation, Preterm

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Systemic sclerosis or scleroderma is a connective tissue disease in which skin tightness is the hallmark of the disease. The disease progression has been subdivided into 3 phases: the edematous, indurative, and atrophic phase[1]. The edematous phase is the early phase of the disease and the initial presentation can include puffy hands, sclerodactyly, and/or Raynaud's phenomenon[1]. Skin tightness is the classical presentation in the indurative phase and the extent of skin tightness is classified into two major subsets: viz., limited cutaneous systemic sclerosis [lcSSc], and diffuse cutaneous systemic sclerosis [dcSSc][1].

The prevalence of the disease is common in woman between 40 and 50 years of age; however, it can occur during the reproductive years[2,3]. The study showed that SSc itself does not affect hormone production or folliculogenesis in SSc patients, so they can achieve spontaneous pregnancy without assisted fertility. Notwithstanding, there are many factors that can affect the pregnancy plan and outcome among SSc patients; particularly physical factors including limitation of joint movement and dyspnea due to pulmonary fibrosis or pulmonary arterial hypertension [PAH]. Moreover, psychological factors (i.e., anxious in self-image and poor self-esteem) can influence fertility and family planning; thus, reproduction in persons with SSc trends to be lower than in the normal population.

There are very few studies on pregnancy outcomes in SSc patients because most SSc patients are diagnosed during menopause or the SSc patients chose to avoid/not to attempt pregnancy. Around 0.04% of the patients diagnosed with SSc had more frequent pregnancy complications than normal pregnancy (OR 4.57 (95%C I 1.57 to 13.57)[4]. Pulmonary arterial hypertension and renal crisis were the major

Correspondence to:
Foocharoen C. Department of Medicine, Faculty of Medicine Khon Kaen University, Khon Kaen 40002, Thailand.
Phone: +66-43-363746, +66-43-363664
E-mail: fching@kku.ac.th

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organ involvements having an impact on feto-maternal health and pregnancy outcome[5].

The study revealed that 29% of pregnant SSc patients miscarried vs. 17% of general pregnancies. The dcSSc group had a higher rate of miscarriage than the lcSSc group. The pathophysiology of miscarriage is not well understood[6,7]; it is thought to be related to intrauterine and/or placental vasculopathy[8].

Other studies revealed that 50 to 63% of SSc patients had stable disease throughout pregnancy period, while 20 to 25% experienced disease improvement and 17% disease worsening[6,9]. The common clinical features of SSc found or worsened during pregnancy were gastroesophageal reflux, Raynaud's phenomenon, arthritis, and/or progressive skin tightness[5,9-11]. Gastroesophageal reflux, Raynaud's phenomenon, and skin tightness were reported to worsen during the third trimester[7]. Some studies have shown that the SSc patients who got pregnant within 5 years of disease onset had a higher rate of complications than those who got pregnant more than 5 years after onset[6,10]. The finding could be related to the high prevalence of internal organ involvement in the first 5 years of the disease[12-14].

Owing to the dearth of studies addressing pregnancy outcomes in SSc and the different clinical features of SSc between Thai (mostly the dcSSc subset) and Caucasian (mostly the lcSS subset), we sought to determine the pregnancy outcomes among Thai patients with SSc.

Materials and Methods

A 11-year retrospective study was conducted at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. Included in the study were scleroderma patients who were pregnant between January 1, 2007 and December 31, 2017 and followed-up at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand.

Operational definition

A diagnosis of systemic sclerosis [SSc] was based on the criteria set out by the American College of Rheumatology[15]. SSc was classified as the limited or diffuse type, according to the classification by Le Roy et al[16]. The duration of disease at pregnancy was counted from the date of last menstrual period [LMP] and the date of the first symptom(s) of SSc.

The intrauterine growth restriction [IUGR] is the definitive criterion as set by the American College of Obstetricians and Gynecologists[17]. IUGR is described as an estimated fetal weight in the 10th percentile for gestational age.

A non-stress test [NST] was used to classify reactive vs. non-reactive disease. Reactivity was defined as a normal fetal heart rate between 110 and 160 bpm and two or more accelerations within a 20-minute period, without any decrease in fetal heart rate[18].

Statistical analysis

The data were divided into dichotomous or polytomous or continuous variables. Codes were used for each categorical variable. The respective continuous data were presented as a mean (standard deviation; SD) or median (interquartile ranges; IQR) as appropriate. The respective categorical data were presented as a proportion or percentage. The data were analyzed using STATA version 11.2 (StataCorp., College Station, TX, USA).

The study was reviewed and approved by the Human Research Ethics Committee of Khon Kaen University as per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE611107).

Results

Seven pregnancies from five SSc women were reviewed. The age of pregnancy was between 23 and 37 years. The duration of diagnosed SSc prior to getting pregnant ranged from 1 month to 7 years, and 1 person was diagnosed during the pregnancy. Most (4 of 5) of the patients had the lcSSc subset and two had overlap with other connective tissue diseases. The majority of subjects were positive for the anti-topoisomerase antibody. Only one patient had pulmonary fibrosis before getting pregnant and she continued her pregnancy without any worsening of WHO functional class or progression of pulmonary fibrosis. The patients having SSc overlap with other connective tissue disease needed high-dose steroid therapy or immunosuppressant therapy throughout the pregnancy while only low-dose steroid therapy was given to patients with pure SSc. The clinical characteristics before getting pregnant and during pregnancy are presented in Table 1.

Four of seven SSc pregnant required pregnancy termination. One of women with SSc had been pregnant three times and was first diagnosed with SSc overlap with systemic lupus erythematosus during her first pregnancy. During the pregnancy included in the current study, she required pregnancy termination due to uncontrolled disease. Two years after being

Table 1. Clinical characteristics and pregnancy outcome

Data	Case 1			Case 2	Case 3	Case 4	Case 5
	Pregnancy No.1	Pregnancy No.2	Pregnancy No.3				
Age at pregnancy (years)	25	27	30	33	23	37	26
Duration of disease at pregnancy	1 month	2 years	5 years	7 years	3 years	Disease onset during pregnancy GA 34 weeks	4 years
SSc Subset	lcSSc overlap SLE				lcSSc	lcSSc	dcSSc
lcSSc overlap PM							
Serology							
Anti-topoisomerase antibody	Positive	Positive	Positive	Positive	Negative		
Anti-Ro52 antibody	Not done	Not done	Not done but anti-Ro positive	Negative	Negative	Not done	Negative
Clinical characteristic before pregnant							
SBP/DBP (mmHg)	95/54	ND	130/54	118/56	117/65	130/80	99/65
Body mass index (kg/m^2)	19.8		21.6	26.2	19.3	20.6	20.4
WHO Functional class	I	I	I	I	I	II	I
Raynaud's phenomenon	Yes	No	No	Yes	Yes	Yes	No
Pulmonary fibrosis	No	No	No	Yes	No	No	No
Pulmonary arterial hypertension	No	No	No	No	No	No	No
Esophageal involvement	No	No	No	No	No	No	No
Intestinal symptom	No	No	No	No	No	No	No
Renal crisis	No	No	No	No	No	No	No
Proteinuria	No	No	No	No	No	No	No
Modified Rodnan skin score	ND	ND	ND	9	10	10	4
Autoimmune hemolytic anemia	Yes	No	No	No	No	No	No
Treatment							
Prednisolone	60 mg/d	10 mg/d	10 mg/d	No	10 mg/d	No	10 mg/d
Immunosuppressant	No	No	No	No	No	No	Azathioprine 50 mg/d

SSc systemic sclerosis, SLE systemic lupus erythematosus, PM polymyositis, SBP systolic blood pressure, DBP diastolic blood pressure, GA gestational age, ND no data available, PROM premature ruptured of membrane

*follow up and delivery at another center, ** IUGR intrauterine growth restriction

Table 1. Cont.

Data	Case 1			Case 2	Case 3	Case 4	Case 5
	Pregnancy No.1	Pregnancy No.2	Pregnancy No.3				
Age at pregnancy (years)	25	27	30	33	23	37	26
Duration of disease at pregnancy	1 month	2 years	5 years	7 years	3 years	Disease onset during pregnancy GA 34 weeks	4 years
Active organ involvement during pregnancy							
Raynaud's phenomenon	No	ND*	No	Yes	Yes	Yes	No
Pulmonary fibrosis	No	ND*	No	Yes	No	No	No
Pulmonary arterial hypertension	No	ND*	No	No	No	No	No
Esophageal involvement	No	ND*	No	Yes	No	Yes	No
Intestinal symptom	No	ND*	No	No	No	No	No
Renal crisis	No	ND*	No	No	No	No	No
Proteinuria	No	ND*	No	No	No	No	No
Autoimmune hemolytic anemia	Yes	ND*	Yes at GA 36 weeks	No	No	No	No
Treatment							
Prednisolone	60 mg/d	ND*	60 mg/d	No	10 mg/d	No	10 mg/d
Immunosuppressant	No	ND*	No	No	No	No	Azathioprine 25 mg/d
Gravida	1	2	3	2	1	1	1
Pregnancy complication	-	No	Eclampsia	Preterm pregnancy	Preterm pregnancy	Fetal distress	PROM
Non-stress test	-	ND*	Reactive	Not done	Not done	Not done	Not done
Mode of delivery	Termination	Normal delivery	Termination	Normal delivery	Normal delivery	Termination	Termination
Gestational age during delivery or terminated pregnancy(weeks)	8	38	37	34	36	35	35
Baby weight (gram)	-	2,560	2,120**	2,000	2,350	1,470**	2,100

SSc systemic sclerosis, SLE systemic lupus erythematosus, PM polymyositis, SBP systolic blood pressure, DBP diastolic blood pressure, GA gestational age, ND no data available, PROM premature ruptured of membrane

*follow up and delivery at another center, ** IUGR intrauterine growth restriction

diagnosed and after controlling the disease, she had a normal term pregnancy and delivered without complications (i.e., the baby had a normal body weight and no anomalies). In another pregnancy, she had severe complications at 37 weeks of gestation (i.e., eclampsia with hemolytic elevated liver enzyme and low platelet [HELLP]) so the pregnancy was terminated. The baby was diagnosed IUGR. Other pregnancies were terminated due to fetal distress and premature rupture of the membrane (Table 1). None of the delivered pregnancies had any detectible fetal anomalies.

Pre-term delivery occurred in 2 pregnant SSc patients. The SSc disease did not worsen or progress during the pregnancy in either patient, and both the maternal and fetal outcomes were normal. The body weight of babies was above the 10th percentile for their gestational age.

Discussion

The number of pregnant SSc patients in our 11-year retrospective study was low. The result is not surprising since the peak incidence of the disease does not fall within the reproductive age, and the majority of patients are in menopause. Most of our SSc pregnant patients had mild disease severity i.e., no extensive skin tightness and less internal organ involvement so, the disease did not complicate the pregnancy.

Some of the SSc patients, however, had to terminate the pregnancy. The reasons for termination were uncontrolled disease, fetal distress, and premature rupture of membrane. The high rate of termination might be explained by unplanned pregnancy particularly in those who had uncontrolled disease (2 terminations in 1 patient). None of the term pregnancies had any fetal anomaly detected, which might be the result of less frequent use of immunosuppressants or teratogenic drugs in those patients.

Fetal distress occurred in those diagnosed with dcSSc during pregnancy. The patient had mild skin tightness and no serious internal organ involvement, but she had uncontrolled Raynaud's phenomenon during pregnancy (before diagnosis SSc). As is known, dcSSc has a high disease severity (including extensive skin tightness, severe vasculopathy and internal organ involvement)[19] and the degree of vasculopathy may lead to placental insufficiency[20–22]. We were not, however, able to conclude whether or not the fetal distress in the dcSSc patient was related to vasculopathy because there was no histopathology of the placenta.

Although SSc is a systemic connective tissue disease and fibrosis and vasculopathy are the main pathophysiology of the disease, two-thirds of patients diagnosed as pure SSc are able to continue their pregnancy without complications. Even when patients had pre-term deliveries, the babies were of an appropriate weight without IUGR. A previous study found that pre-term delivery in SSc was not related to the severity of disease but may be the result of abnormal connective tissue[23]. Due to the low number pregnant of SSc patients in our study, we were not able to determine the association between pre-term delivery and SSc. According to our observations, the outcome of pregnancy in SSc patients particularly those with mild skin tightness (the lcSSc subset) and no internal organ involvement is good. It is possible that the well-controlled lcSSc patient is a candidate for pregnancy, however, the attending physician should be aware of the potential for pre-term labour among this subgroup of patients and family planning is suggested for all reproductive age SSc patients.

The present study had some limitations. First, the study used retrospective data collection, so there were some missing data. Second, there was a low number of women with SSc getting pregnancy. Due to the low prevalence of SSc during the reproductive age, we cannot generalize the association between clinical features of the disease and complications during pregnancy. Third, the placental histopathology was not defined, so the etiology of fetal distress cannot be definitively stated. Notwithstanding, our preliminary data have some value for evaluating SSc patients with pregnancy in Thailand; in order to determine the maternal and fetal outcome. Ultimately, the data can be used for devising better care of pregnant SSc patients.

What is already known on this topic?

There are few studies of pregnancy outcome among SSc patients because most of the patients are diagnosed SSc during menopause or patients choose not to get pregnant. Around 0.04% of patients are diagnosed with SSc during pregnancy and this subgroup has more frequent pregnancy complications than normal pregnancies. Pregnancy outcomes among Thai women with SSc (usually the dcSSc subset) have not been reported.

What this study adds?

There were few pregnancies among women with SSc over the 11 years of this historical review. Most of the SSc patients had an uncomplicated pregnancy but maternal and fetal outcomes in those

with SSc overlap with other connective tissue disease were not as good as those with pure SSc. Family planning is suggested for all reproductive age SSc patients.

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Author contributions

All of the authors have read and prepared the manuscript.

Potential conflicts of interest

The authors have no conflicts of interest.

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