Systemic sclerosis and hyperthyroidism in pregnancy

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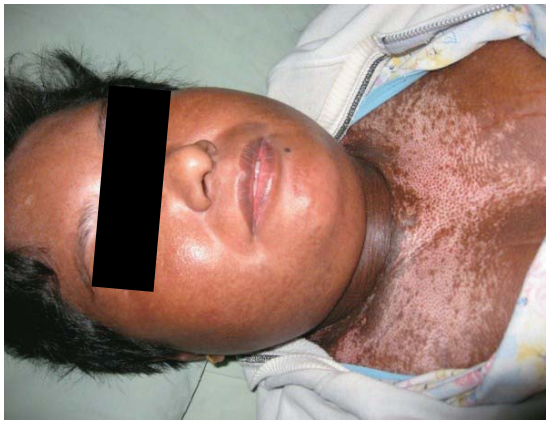
Systemic sclerosis (SSc) is a connective tissue disease affecting women of childbearing age at least five times more than men. For a long time, pregnant women with SSc have high morbidity and mortality based on case reports and case series. Therefore, the disease was a contraindication for pregnancy. However, current retrospective studies show that despite of an increased frequency of prematurity and small for gestational age infants, overall maternal and neonatal survival is good. With close monitoring and appropriate therapy, most scleroderma patients can sustain a successful pregnancy.[1,2]

CASE REPORT

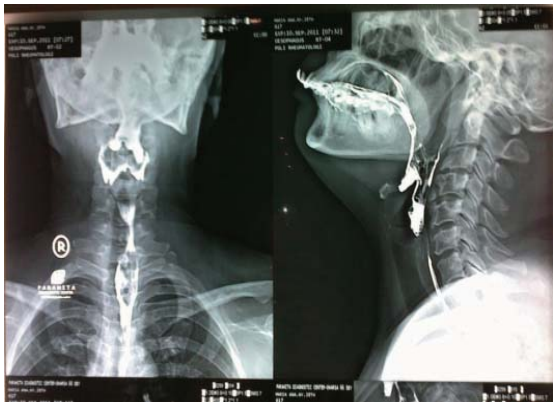
A 38-year-old woman was referred from Kupang, East Nusa Tenggara to rheumatology outpatient clinic because of thickened skin, chronic dry cough, palpitation, and intermittent difficulty in swallowing since 2 years before admission. She had been diagnosed with scleroderma and hyperthyroid. Her medications in Kupang were methylprednisolone 4 mg b.i.d., propylthiouracil 100 mg b.i.d., propranolol 10 mg t.i.d., and amlodipine 5 mg daily. She had been married for 5 years without any history of contraception and pregnancy. Her vital signs were normal. Her pulse rate was 92 beats/min and regular. She had hyperpigmentation and thickening on almost all of her skin. There were also salt and pepper leukoderma (picture 1) and sclerodactyly (picture 2). Her abdomen was slightly distended and she had Raynaud's phenomenon.



Picture 1 Salt and pepper leukoderma

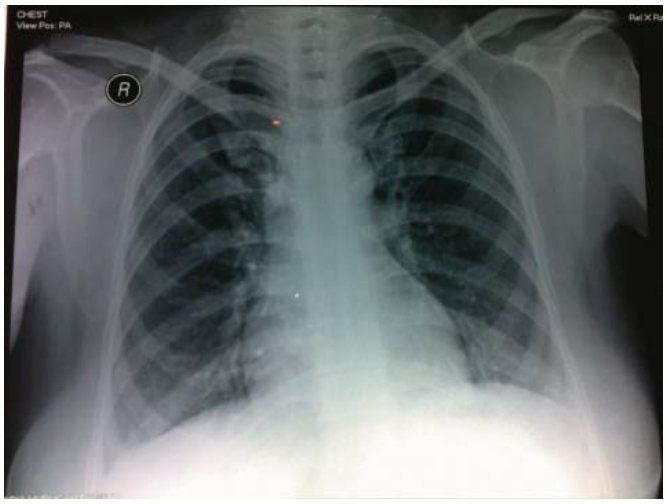
Picture 2 Sclerodactyly

On laboratory examination, we found elevated erythrocyte sedimentation rate (ESR) at 50 mm/hr and leukocytes count of 12.700/mm^3. Her urinalysis resulted in elevated protein level at 75 mg/dL. She also had elevated thyroxine (T4) at 27.1 mcg/dL (normal limit: 4.5 – 10.9) and TSHs at 0.09 mU/L (0.35 – 5.5). She was positive for ANA and Anti-Scl-70, but her IgG and IgM anticardiolipin antibody (ACA) were negative. Her echocardiography, esophagogram (picture 3), and chest x-ray (picture 4) were normal. An ultrasound on her thyroid revealed diffuse enlargement with hypoechoic thyroid lobes associated with heterogenous parenchymal appearance.



Picture 3 Barium esophagogram revealed normal esophageal motility (no esophageal dilatation)

An abdominal ultrasound showed a fetus in her uterus with estimated fetal weight of 1100 grams. It was inconsistent with her history of menstruation, because the pregnancy would have been about 31-32 weeks. Her final diagnosis was systemic sclerosis with hyperthyroidism, pregnancy, and intrauterine growth retardation (IUGR). Her



Picture 4 No abnormality detected in the Chest X-Ray

methylprednisolone dosage was changed into once daily in the morning and her propranolol was stopped. She was also consulted to an obstetrician. It was later decided that she was pregnant for 27-28 weeks based on her USG result.

A month later, the patient came with chief complaint of palpitation, diarrhea, and prolonged cough. She was admitted and observed for the possibility of a thyroid crisis. Her vital signs showed blood pressure at 120/ 80 mmHg, heart rate at 122 beats/ minute, respiration rate at 20 times/ minute, and temperature at 36.8 ^{0}C. She had normal CBC, renal function test, ECG, and stool examination. Her ESR was at 40 mm/ hr and her albumin level was at 2.5 mg/dL. She had elevated thyroxine (T4) at >30 mcg/dL and TSHs at 0.741 mU/L. Her Burch Wartovsky score was 35 (22–44 means impending thyroid crisis). Supportive therapy was given and her conditions improved. She also had monitoring of fetal heart beat every 6 hours and fetomaternal ultrasonography weekly.

Two weeks later, the patient had a fever, cough, and shortness of breath. There were crackles in both lower lobes of her lungs. Her leukocytes count was 12.300/ mm^3 and her chest X ray showed honeycomb appearance in lower lobes of her lung. She was diagnosed with pneumonia but interstitial lung disease was thought of as a differential diagnosis. Antibiotic was given for a week. Her conditions improved, but there was a worsening of fetal's non-stress test (NST) and she needed caesarean section. She gave birth to a 1300 grams baby boy with length of 36 cm and Apgar Score 8/9. Five days later, she was discharged from the hospital. The therapy was continued with additional azathioprine 50 mg b.i.d.

Ten days after, the patient was admitted again due to fever and shortness of breath. Her blood pressure was 100/60 mmHg, pulse rate was 92 beats/minute, respiration rate was 28 times/minute, and temperature was 38 ^{0}C. Her surgery scar was in good condition. There were crackles in both lower lobes of the lung and her chest x-ray result was the same as before. The laboratory result came back with anemia (8.6 g/ dL), low albumin (2.3 mg/dL), normal leukocyte count (9,260/ mm^3) normal platelet count (233,000/mm^3), and elevated ESR (55 mm/hr). Again the patient was diagnosed with pneumonia and interstitial lung disease as differential diagnosis. Sputum, urine, and blood culture were performed. She was also scheduled for chest high resolution CT scan and pulmonary function test. While waiting for results, she had oxygen 8 L/ min, intravenous levofloxacin 750 mg daily, and nebulizer.

A week later, the fever subsided, but her cough and dyspnea worsened. The sputum, urine, and blood culture were all negative. She was then given intravenous cyclophosphamide 500 mg in addition to her ongoing therapy. Three days later, the patient still had dyspnea with increased heart rate (130 times/ minute) and respiration rate (39 times/ minute). Her blood gas analysis showed severe hypoxia with type I respiratory failure. There was no chance for assisted ventilation as she suddenly had cardiac arrest and died.

Her baby had neonatal jaundice and sepsis after about 1.5 month in incubator, but with proper treatment he was finally discharged from the hospital without any episode of hypothyroidism.

DISCUSSION

Scleroderma is a connective tissue disease of unknown etiology that afflicts the lungs, heart, gastrointestinal tract, and kidneys. It is a relatively rare disease with an estimated incidence rate ranging from 2 to 10 cases per million. The etiopathogenesis of scleroderma includes vascular dysfunction, mononuclear mediated inflammation, and connective tissue fibrosis.[2]

Examination for thyroid dysfunction is important in scleroderma as many symptoms of hypothyroidism and hyperthyroidism overlap with scleroderma features. Thyroid fibrosis, autoimmune thyroiditis resulting in hypothyroidism, and hyperthyroidism from Graves' disease are frequent and often unsuspected in scleroderma. Fibrosis of the thyroid gland may develop in the presence or absence of autoimmune thyroiditis. In a Hungarian population, the prevalence of Hashimoto's thyroiditis and Graves' disease was 220-fold higher and 102-fold higher, respectively, in scleroderma patients than in the general population. In particular, anti-thyroid peroxidase (anti-TPO) antibodies are more commonly observed in scleroderma than in controls, and it has been suggested that anti-TPO antibodies may identify the subset of patients at risk for subsequent thyroid dysfunction. It suggests that assessment of thyroid function and anti-TPO antibodies should be done in routine clinical evaluations of patients with scleroderma.[3,4] In this case, the cause of hyperthyroidism was possibly Grave's disease, because thyroid gland fibrosis usually manifests as hypothyroidism. However, there was no examination of thyroid antibodies due to lack of reagent in the hospital. With anti-thyroid drug (propylthiouracil), she became euthyroid.

Effects of scleroderma on women fertility

The patient had been married for five years without any history of pregnancy and contraception (primary infertility). Her irregular menstrual period could be due to the SSc itself or her hyperthyroidism. The issue of fertility in women with SSc is also difficult to determine because there are many factors, both physical and psychological, affecting pregnancy. Reduced self esteem and altered body image may have great

impact to the ability of patients with scleroderma to form social and sexual relationships. The disease poses further difficulties to interpersonal relationships due to vaginal dryness and dyspareunia which afflicts up to 37% of patients, as well as arthritic involvement and joint contractures which may prevent sexual intercourse. However, there were no specific findings causing infertility that could be attributed specifically to SSc.[2,5]

Women with scleroderma have twice the rate of spontaneous abortion and three times the rate of infertility (no successful pregnancy up to the age of 35) compared with normal women. The overall rate of a successful pregnancy following a period of infertility was 37% in the scleroderma patients, similar to the 40% rate in RA patients and 43% in normal controls.[2]

Effects of scleroderma and hyperthyroidism on pregnancy

The reported outcomes of pregnancy in women with SSc were quite variable. Early literatures were filled with case reports of SSc on pregnancy that resulted in unfavorable outcomes to the mother and/or the baby.[5] But nowadays close monitoring and appropriate therapy helped scleroderma patients to have a successful pregnancy. In this patient, there were some obstetric complications such as IUGR, premature labor, and the need of emergency caesarean section.[6,7] As seen in table 1, those three are the most frequent obstetric complications in SSc patients.

Table 1 Pregnancy complications in SSc compared with GOP[6]

	SSc n(%)	GOP* n(%)	P (SSc vs GOP)
Deliveries, n°	106	3939	
Intrauterine growth restriction (IUGR) (<5th percentile)	**6 (6%)**	**58 (1%)**	**p=0,005**
Preterm premature rupture of membrane	7 (7%)	126 (3%)	NS
Preterm deliveries <37 weeks	**32 (30%)**	**470 (12%)**	**p<0,001**
Cesarean section	**54 (51%)**	**1222 (31%)**	**p<0,001**
Gestational hypertension	1 (1%)	123 (3%)	NS
Pre-eclampsia/HELLP	1 (1%)	43 (1%)	NS
Eclampsia	0 (0%)	0 (0%)	NS

*GOP: Data from General Obstetric Population followed in 2009 in one of the referral centers

Patients with diffuse skin involvement suffered from more significant morbidities, with premature delivery dominating 40% of pregnancies. Despite all of the possible complications, the overall rate of successful delivery was 84% in limited and 77% in diffuse scleroderma.[2]

A study for over 12 years involving 60 cases of hyperthyroidism on pregnancy in University Hospital of Wales UK found that metabolic status at delivery correlated with pregnancy outcome. Preterm delivery, perinatal mortality, and maternal heart failure were more common in women who remained thyrotoxic even with clear diagnosis and treatment.[8] In this patient, she already had hyperthyroidism before her pregnancy and anti-thyroid therapy (PTU) was continued during pregnancy.

Effects of pregnancy on scleroderma and hyperthyroid

In pregnancy, there is an increase of T helper-2, which allows a woman's body to tolerate the fetus, and this is thought to be the reason why the severity of Graves' hyperthyroidism (and other autoimmune diseases) usually lessens after the first trimester [9]. On rare occasions, labour, caesarean section, and infections may aggravate hyperthyroidism into thyroid storm. Most pregnant women with hyperthyroidism have already been diagnosed prior to pregnancy and they tolerate mild to moderate degrees of hyperthyroidism relatively well. Graves may be exacerbated in the early parts of pregnancy, but as immune suppression typically occurs with the pregnancy, the disease becomes less active. After delivery, they may remain in permanent remission, but recurrence is also possible.[8,10] In this patient, there was an impending thyroid crisis that could be induced by infection (pneumonia), but she became euthyroid at the end period of pregnancy by using propylthiouracil 100 mg t.i.d. and there was no episode of recurrence postpartum.

Pregnancy appears to exacerbate organs involvement or adversely affect 10 year survival of scleroderma patients. In a prospective series, maternal disease was stable in 60% of cases, improved in 20%, and worsened in another 20%. However, the enlarging gravid uterus may worsen gastroesophageal reflux, which is a prevalent symptom in scleroderma. Likewise, limitation of diaphragmatic breathing may exacerbate pre-pregnancy dyspnea.. On the other hand, Raynaud's phenomenon tends to improve in pregnancy due to generalized peripheral vasodilation. Even though pregnancy is not considered to worsen skin disease, progressive skin thickening has been observed in the postpartum women with diffuse disease. As women with diffuse scleroderma are at greater risks for early cardiopulmonary and renal problems, they need to delay pregnancy until their organ functions are stable.[2] Generally, effects of pregnancy on scleroderma can be seen in table 2 below.[5]

Table 2 Effects of pregnancy on systemic sclerosis

SSc involvement	Changes during pregnancy
General	Stable
Raynaud's phenomenon	Improved during pregnancy, worsen after/ during complicated deliveries
Skin	possibility of onset during pregnancy and progressive involvement in postpartum with diffuse SSc
Joints	arthralgia, similar to pregnant women without scleroderma
Gastrointestinal	reflux, similar to pregnant women without scleroderma
Cardiopulmonary	Worsening shortness of breath and should be managed as in any pregnancy with compromised cardiopulmonary status
Kidney	Renal crisis occurs during early diffuse scleroderma with or without pregnancy. Should be managed with ACE-inhibitors despite the fetal risks

Pregnant women with scleroderma are at high risks because of their possibility of having premature delivery and other maternal complications, most notably scleroderma renal crisis (SRC). Initial risk assessment should include disease grading, as women with diffuse disease are at higher risk for miscarriage, preterm delivery, and SRC.[2]

Management of scleroderma and hyperthyroidism in pregnancy

Management of scleroderma patients during pregnancy, labor, and delivery can be seen in the table 3 below.[5]

Table 3 Management of scleroderma patients during pregnancy, labor, and delivery[5]

Preterm

1. Early evaluation of the extent of organ involvement and autoantibody analysis, including echocardiogram and pulmonary function if necessary
2. Discontinue the use of disease-remitting drugs with teratogenic potential (i.e., MMF, methotrexate, etc.) before pregnancy
3. High-risk obstetric care
4. Reassurance to the mother
5. Minimal use of proton pump inhibitors, histamine antagonist, or calcium-channel blockers for gastrointestinal and vascular problems
6. Avoidance of corticosteroids
7. frequent monitoring of fetal size and uterine activity
8. Frequent blood pressure monitoring
9. Aggressive treatment of hypertension
10. Close observation and treatment for premature labor (avoid beta-adrenergic agonists)

Labor and delivery

1. Epidural anesthesia is preferred
2. Warming of delivery room, intravenous fluid, and the patients themselves (e.g., extra blankets, thermal socks, gloves)
3. Venous access before delivery
4. Careful attention to the episiotomy and incisions, which generally heal without difficulty

Post delivery

1. Continue careful monitoring postpartum, with early reinstitution of medication and aggressive treatment of hypertension

There is no data regarding the preferred method of delivery in scleroderma patients and the decision should be made based on a joint consultation of the inter-disciplinary team. When there is no fetal distress, pulmonary, cardiac, or renal involvement and the patients have good range of motion of hip joints, vaginal delivery is the better choice. One should also keep in mind that severe restrictive lung disease may exist in patients without alveolitis due to established lung fibrosis as well as chest-wall involvement. Performing pulmonary function tests during the first trimester, and if needed, repeating them in later stages of pregnancy, is advisable. The presence of major organ involvement or severe musculoskeletal restriction may emerge the need to have cesarean section.[2] In this case; the indication of cesarean section was fetal distress.

When organs are severely damaged, such as in cases of severe cardiomyopathy (ejection fraction <30%), pulmonary hypertension, severe restrictive lung disease (forced vital capacity <50%), malabsorption, or renal insufficiency, the decision to terminate the pregnancy may have to be considered depending on the risks to the mother and the fetus.[5] In this case, her heart and kidney were normal and there was no sign of scleroderma renal crisis. Unfortunately, there was no chance to perform chest HRCT and pulmonary function test. The dyspnea worsened 10 days after delivery and she had been given intravenous cyclophosphamide, but it did not help (maybe too late), she got respiratory failure and died.

Interstitial lung disease (ILD) is a common manifestation of SSc and mainly encountered in patients with diffuse disease and/or anti-topoisomerase 1 antibodies. ILD is now the major cause of mortality in patients with SSC after dramatic reduction in death caused by scleroderma renal crisis, because of the regular use of ACE inhibitors. Although it is important to treat ILD in SSc early, but progression of lung involvement may be variable and difficult to predict. ILD develops in up to 75% of patients with SSc overall. However, SSc-ILD evolves to end-stage respiratory insufficiency in only a few patients. Initial pulmonary function tests (PFT) with measurement of carbon monoxide diffusing capacity, together with HRCT, allows for early diagnosis of SSc-ILD, before the occurrence of dyspnea.[11,12] This patient had a diffuse disease and her anti-topoisomerase 1 antibodies (Anti-Scl-70) was also positive, making her prone to have ILD. The progress of the ILD was quite fast. In a week she had become worse, fell into respiratory failure despite of intravenous cyclophosphamide.

SUMMARY

This is a case report about a pregnant woman with scleroderma and hyperthyroidism. There were some obstetric complications such as IUGR, premature labor, and the need of emergency cesarean section, but the pregnancy was ended successfully. Unfortunately 10 days after delivery she was admitted again into the hospital due to rapid progressive ILD. Although intravenous cyclophosphamide had been administered, she fell into respiratory failure and died. After about 1.5 month of care in NICU due to low body weight, neonatal jaundice, and sepsis, the baby was discharged without significant abnormality.

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