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Obstetrical Success of a Very High-Risk Pregnancy in a Patient with Severe Systemic Sclerosis and a History of Three Fetal Deaths and One Neonatal Death

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Abstract

This case report describes the successful multidisciplinary management, within a specialized facility, of a very high-risk pregnancy in a 42-year-old patient with systemic sclerosis (SSc). The disease was stable under azathioprine (150 mg/day) and characterized by double immunological positivity (ANA, anticentromere) along with severe dual involvement: mucocutaneous and interstitial lung disease (pure restrictive ventilatory defect with TLC < 51%). Despite a tragic obstetric history marked by three fetal deaths and one early neonatal death, intensive bi-weekly maternal-fetal monitoring involving obstetricians, internists, cardiologists, and pulmonologists maintained maternal systemic stability (with no scleroderma renal crisis or pulmonary arterial hypertension) and ensured harmonious fetal growth (eutrophic fetus). At the end of the third trimester, given the major risk of maternal respiratory exhaustion during pushing efforts and the strict contraindications to general anesthesia (risks of difficult intubation due to oral sclerosis, aspiration pneumonitis due to severe gastroesophageal reflux, and acute PAH flare-up during induction), a prophylactic cesarean section under spinal anesthesia was planned. The spontaneous onset of labor at 36 weeks and 6 days prompted an emergency performance of the procedure, leading to the birth of a healthy female infant weighing 2950 g with an Apgar score of 10/10 and uneventful postoperative recovery.

Keywords

Systemic Sclerosis, High-Risk Pregnancy, Azathioprine, Interstitial Lung

Disease, Intrauterine Fetal Death (IUFD)

1. Introduction

Systemic sclerosis (SSc) is a rare auto-immune connective tissue disorder characterized by diffuse microangiopathy and progressive fibrosis affecting the skin and internal organs, primarily the lungs, gastrointestinal tract, and heart [1]. Affecting predominantly women of childbearing age, it has long been considered a contraindication to pregnancy due to historically dismal maternal-fetal outcomes [2].

Although SSc does not directly impair fertility, it significantly increases the risk of adverse pregnancy outcomes (APO). More than a quarter of pregnancies in these patients face vascular or placental complications, such as pre-eclampsia, intrauterine growth restriction (IUGR), or intrauterine fetal death (IUFD) [3]. Management is further complicated by the dual challenge of maintaining strict immunosuppressive control compatible with gestation (such as azathioprine) and managing maternal visceral damage—particularly pulmonary involvement—which dictates anesthetic choices and the mode of delivery [2].

We report the case of a 42-year-old patient with SSc presenting with severe mucocutaneous and restrictive pulmonary involvement. Despite a tragic obstetric history marked by three fetal deaths and one early neonatal death, a highly coordinated multidisciplinary strategy achieved a successful outcome. This case underscores the paramount importance of intensive surveillance and transdisciplinary synergy in reversing an initially poor obstetrical prognosis.

2. Case Presentation

A 42-year-old female patient, gravida 5 para 5 with a significant obstetric history marked by three unexplained intrauterine fetal deaths (IUFD) and one early neonatal death, was admitted to our facility. She had been monitored since 2015 for systemic sclerosis (SSc) with dual visceral involvement: severe interstitial lung disease—treated in 2016 with six pulses of cyclophosphamide (Endoxan)—and mucocutaneous involvement, which required a corticosteroid regimen of 60 mg/day of prednisone (discontinued in 2022). Her long-term maintenance therapy consisted of azathioprine (Imurel) at a dosage of 150 mg/day (one 50 mg tablet three times daily), which was continued due to its safety profile during pregnancy.

The patient's history of three intrauterine fetal deaths may have resulted from chronic uteroplacental insufficiency related to maternal vasculopathy in the setting of systemic sclerosis. Indeed, systemic sclerosis is characterized by diffuse microvascular damage and endothelial dysfunction, both of which can compromise fetoplacental perfusion and exchange, thereby predisposing to fetal growth restriction, chronic fetal hypoxia, and, ultimately, intrauterine fetal demise. This risk may have been further exacerbated by the autoimmune background, advanced maternal age, and the severity of the maternal systemic involvement.

The initial consultation at our unit occurred at 12 weeks of gestation. The first-trimester ultrasound scan revealed a viable singleton intrauterine pregnancy with a crown-rump length (CRL) corresponding to 12 weeks and 3 days of gestation. The initial standard and specific laboratory workup (please refer to the appendix for the results) included a complete blood count and platelet count (CBC-Plt), coagulation profile, renal function tests, fasting plasma glucose, thyroid-stimulating hormone (TSH), blood typing, irregular antibody screening, and a comprehensive autoimmune panel (including antinuclear antibodies [ANA], anti-Scl70, and antiphospholipid syndrome screening).

Given the systemic nature and progressive potential of SSc, a multidisciplinary approach was implemented, including monthly evaluations by cardiology, internal medicine, and pulmonology teams. The baseline transthoracic Doppler echocardiography showed a preserved left ventricular ejection fraction (LVEF) of 70%, with no signs of pulmonary arterial hypertension (PAH). Pulmonary function tests (PFTs) revealed a pure restrictive ventilatory defect without an obstructive component, characterized by a total lung capacity (TLC) below 51% of the predicted value. Arterial blood gas analysis demonstrated well-compensated chronic respiratory alkalosis. Considering the clinical stability of the mucocutaneous and pulmonary lesions, the internal medicine team recommended continuing azathioprine at the same dosage.

Starting from the second trimester, the frequency of prenatal visits was increased to every two weeks for close maternal and fetal surveillance. The anomaly scan at 22 weeks of gestation was normal, with an estimated fetal weight (EFW) of 500 g (matching physiological percentiles). Throughout follow-up, fetal growth remained appropriate for gestational age (eutrophic fetus), and uterine, umbilical, and cerebral artery Doppler indices remained within physiological ranges. Maternal renal function remained stable, with a strictly physiological 24-hour urine protein level of 0.11 g/24 h.

At 26 weeks and 5 days of gestation, the patient was hospitalized for an acute bronchial syndrome. Sputum cultures (ECBC) returned negative. The condition resolved favorably under symptomatic treatment, without any impact on the underlying lung or muscle lesions. Systemically, no scleroderma renal crisis was recorded (normal blood pressure, no degradation of the estimated glomerular filtration rate [eGFR], and absence of proteinuria or hematuria).

A multidisciplinary consultation (involving obstetricians, internists, anesthesiologists, and pediatricians) at the end of the third trimester established an indication for a scheduled cesarean delivery at 37 weeks of gestation under spinal anesthesia. Vaginal delivery was contraindicated due to the high risk of maternal respiratory exhaustion during pushing efforts superimposed on severe restrictive lung disease. General anesthesia was formally rejected due to the risks of difficult intubation (limited mouth opening secondary to mucocutaneous sclerosis), aspiration pneumonitis (severe gastroesophageal reflux disease associated with SSc), and an acute PAH flare-up during induction.

The patient was admitted at 36 weeks and 6 days of gestation for the scheduled procedure. During hospitalization, she went into spontaneous labor, requiring an emergency cesarean section. She delivered a healthy female newborn weighing 2950 g, with an Apgar score of 10/10 at 1 and 5 minutes. The immediate postoperative course was uneventful. The patient was discharged on postpartum day 3, with a strict follow-up schedule coordinated across cardiology, internal medicine, and pulmonology clinics.

Postpartum follow-up was reassuring, with both mother and infant remaining in good clinical condition after hospital discharge. The mother showed no evidence of respiratory decompensation, pulmonary hypertension, renal crisis, or postpartum flare of systemic sclerosis, while the newborn demonstrated normal growth and an uncomplicated early neonatal course.

3. Discussion

Systemic sclerosis (SSc) is a connective tissue disease with a complex and still imperfectly understood pathophysiology. It is characterized by diffuse microangiopathy and progressive fibrosis preferentially targeting the skin, lungs, and gastrointestinal tract [3] [4]. This condition predominantly affects women, with a sex ratio estimated between 3:1 and 8:1 in the literature [5], and a mean age at diagnosis typically ranging between 40 and 45 years [2] [4]. However, the clinical profile of our patient presents atypical features compared to these epidemiological data. On one hand, the disease onset occurred early, at the age of 27. On one the other hand, the initial clinical presentation was strictly limited to mucocutaneous and pulmonary manifestations without detectable microangiopathy, thereby contrasting with classic literature descriptions.

The obstetric history of our patient dramatically illustrates the burden of adverse pregnancy outcomes (APO) conventionally associated with connective tissue diseases. Although the overall fertility of patients with SSc does not appear to be significantly impaired prior to diagnosis [6], the impact of the disease on the course of gestation is major. The occurrence of such a severe obstetric history, marked by three unexplained intrauterine fetal deaths (IUFD) and one early neonatal death, falls within the spectrum of the vascular and placental complications of the disease. Recent literature confirms that SSc carries a considerably increased risk of obstetric complications compared to the general population, including spontaneous abortions, intrauterine growth restriction (IUGR), and pre-eclampsia [7]. In our case, however, the fetus demonstrated harmonious intra-uterine growth, with a birth weight of 2950 g. Preliminary results from the French prospective GR2 study underscore that more than a quarter of pregnancies in SSc patients face an obstetric event of cardiovascular or placental origin.

In agreement with data from Betelli *et al.* [8], patients with a history of systemic sclerosis associated with fetal complications derive a major benefit from a multidisciplinary approach involving obstetricians specialized in maternal-fetal medicine, rheumatologists, and pediatricians. This clinical synergy is essential to opti-

mize perinatal prognosis through rigorous screening for signs of placental insufficiency and other vascular complications. Our therapeutic strategy was fully aligned with this integrated collaborative model. The concerted management of our patient by a team comprising obstetricians, internists, anesthesiologists, and pediatricians allowed for optimal control of the systemic disease, early screening for maternal visceral involvement, and close fetal monitoring.

The paraclinical diagnosis of SSc has been profoundly optimized by the integration of early biomarkers and microvascular imaging into the international ACR/EULAR classification criteria [9]. Biologically, the detection of antinuclear antibodies (ANA) constitutes the cornerstone of screening, yielding a sensitivity greater than 95%. Characterizing antigenic specificity—through the mutually exclusive positivity of anti-topoisomerase I (anti-Scl-70), anti-centromere, or anti-RNA polymerase III antibodies—not only possesses major diagnostic value but also dictates the clinical phenotype and the visceral evolutionary profile of the disease [10] [11]. In our case, the diagnosis was confirmed by the simultaneous positivity of ANA and anti-centromere antibodies.

In the case of Mrs. H.E., maintenance therapy with azathioprine was continued due to its safety profile during pregnancy. Belizna *et al.* [12] also reported that azathioprine is frequently considered a safe treatment during pregnancy, although patients must be closely monitored for potential adverse fetal effects. Furthermore, it is essential to balance the risks and benefits of immunosuppressive therapies such as cyclophosphamide; while highly effective for managing severe SSc manifestations, these agents are generally avoided during pregnancy due to their established teratogenic risks.

Vaginal delivery remains the preferred route in SSc in the absence of absolute obstetric indications for a cesarean section. Early epidural analgesia is highly recommended for its protective vasodilatory effect against peripheral vasospasm, whereas general anesthesia should be avoided due to the risks of pulmonary hypertensive crisis and restricted mouth opening [13] [14]. In pregnant women with systemic sclerosis and severe respiratory involvement, particularly those with marked restrictive ventilatory impairment or advanced interstitial lung disease, the mode of delivery should be individualized within a specialized multidisciplinary setting. When prolonged labor and maternal expulsive efforts are considered likely to precipitate respiratory decompensation, planned cesarean delivery may represent a reasonable prophylactic option. In addition, the anesthetic challenges commonly associated with systemic sclerosis—including limited mouth opening, severe gastroesophageal reflux, pulmonary involvement, and potential cardiopulmonary instability—support an anticipatory strategy favoring regional anesthesia whenever feasible, since general anesthesia may carry substantial maternal risk in this setting.

In our patient, vaginal delivery was contraindicated due to the major risk of maternal respiratory exhaustion during pushing efforts superimposed on severe restrictive lung disease. General anesthesia was formally rejected given the risks

of difficult intubation (limited mouth opening secondary to mucocutaneous sclerosis), aspiration pneumonitis (severe gastroesophageal reflux disease associated with SSc), and an acute PAH flare-up during induction. Consequently, these findings established the indication for a prophylactic cesarean delivery at 37 weeks of gestation under spinal anesthesia.

4. Conclusion

Although systemic sclerosis significantly increases the risk of vascular and placental complications, this case demonstrates that optimal disease control with compatible maintenance therapy (azathioprine), targeted screening for visceral involvement, close maternal-fetal surveillance, and active multidisciplinary collaboration (involving obstetricians, internists, anesthesiologists, and pediatricians) can successfully reverse an initially poor obstetric prognosis and ensure a favorable outcome.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest.

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Appendix. Laboratory Results Sheet

Lab work	First trimester	Second trimester	Third trimester
Hb (g/dl)	11.7	11.9	12.5
Platelets	275.000	260.000	324.000
Coagulation workup	PT/aPTT/ Fibrinogen: 100%/27.9/3.28	PT/aPTT/ Fibrinogen 100%/26.9/2.28	PT/aPTT/ Fibrinogen 98%/28/4.28
Urea	0.15	0.24	0.19
Creatinine	5.40	4.07	4.3
AST/ALT	19.8/11.8	27/9	
Fasting blood glucose.	0.86 g/dl	HGPO: Normal	
TSH	0.86		
Toxoplasmosis	Negative	Negative	Negative
Rubella	Negative	Negative	Negative
Syphilis	Negative	Negative	Negative
Ag HBs	Negative	Negative	Negative
VIH 1-2	Negative	Negative	Negative
Blood typing.	O+/O+		
Red blood cell antibody screening	Negative		Negative
24-hour urine protein.	0.20 g/24H	0.	
Antinuclear antibodies (ANA).	400 (<100)		
Anti-Scl-70 antibodies (anti-topoisomerase I antibodies)	21 UI/ml (<20)		
Anti-centromere antibodies	25 UI/ml (<10 - 20)		
Anti-RNA polymerase III antibodies	18 UI/ml (<20)		
Anti-SSA and anti-SSB antibodies	Negative		
Antiphospholipid syndrome (APS) workup	Negative	Negative	Negative
Urinalysis with urine culture / Vaginal swab	Sterile	Sterile	Sterile