Ritodrine-associated Noncardiogenic Pulmonary Edema Diagnosed by Point-of-care Ultrasound: A Case Report of Twin Gestation

CME Credits

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Abstract

Ritodrine hydrochloride, a beta-adrenergic tocolytic agent, can rarely cause acute noncardiogenic pulmonary edema, particularly in patients with multiple gestations or comorbidities. We report a case of a 28-year-old woman with twin pregnancy, type 1 diabetes, and hyperthyroidism that developed acute respiratory distress following ritodrine infusion. Imaging showed pulmonary edema, and point-of-care ultrasound (POCUS) revealed diffuse bilateral B-lines, preserved left ventricular function, and no signs of right heart strain or inferior vena cava plethora. These findings supported a diagnosis of noncardiogenic pulmonary edema. Emergency cesarean section was performed at $31^{+6/7}$ weeks. Postoperatively, the patient's respiratory status improved, and both neonates had favorable outcomes. This case demonstrates the utility of POCUS as a rapid, radiation-free diagnostic tool for differentiating types of pulmonary edema in pregnant patients, enabling timely intervention and potentially improving maternal and neonatal outcomes. It also underscores the importance of vigilant monitoring when using beta-mimetic tocolytics in high-risk pregnancies.

Keywords: Case report, point-of-care ultrasound, pulmonary edema, ritodrine, tocolysis, twin pregnancy

Introduction

Preterm labor, defined as the onset of labor before 37 weeks of gestation, is a significant cause of neonatal morbidity and mortality. Tocolytic agents are commonly administered to suppress uterine contractions, allowing time for administration of corticosteroids to enhance fetal lung maturity and, if necessary, transfer to a tertiary care center with neonatal intensive care facilities.

Among the various tocolytic agents, beta-adrenergic agonists such as ritodrine (Yutopar) have been widely used despite their association with maternal cardiovascular and pulmonary side effects. Although ritodrine has been withdrawn from the market in some countries including the United States, it remains available in parts of Asia and other regions. Pulmonary edema is a rare but potentially life-threatening complication of beta-mimetic tocolytic therapy, with an estimated incidence of 0.3%–4.0% of patients receiving such treatment.

Risk factors for the development of tocolytic-induced pulmonary edema include multiple gestation, underlying maternal cardiac or metabolic disease, excessive intravenous fluid administration, and concomitant use of corticosteroids. The pathophysiology is believed to involve a combination of increased cardiac output, sodium and fluid retention, and altered capillary permeability.

This report presents a case of acute pulmonary edema in a pregnant woman with twins following ritodrine administration for tocolysis, emphasizing the role of point-of-care ultrasound (POCUS) in rapid diagnosis and the

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Abbreviations

IVC	Inferior vena cava
LV	Left ventricle
POCUS	Point-of-care ultrasound
RV	Right ventricle

importance of prompt recognition and management of this serious complication. The educational objective of this case report is to illustrate the application of POCUS in differentiating between cardiogenic and noncardiogenic pulmonary edema in a high-risk obstetric patient, and to review the pathophysiology of beta-agonist-induced pulmonary edema.

Case Report

A 28-year-old woman, gravida 2 para 0 with one previous abortion, presented with preterm contractions at $31^{+6/7}$ weeks of twin gestation. Her medical history was significant for type 1 diabetes mellitus managed with insulin (last glycated hemoglobin 7.2%, reference range 4.0%–5.6%) and hyperthyroidism under medical control with methimazole 5 mg daily (recent thyroid function tests within normal limits). The patient had been receiving regular prenatal care at a local hospital with no significant problems noted before this event.

The patient was admitted for preterm labor and started on ritodrine tocolysis on November 11, 2022. Intravenous fluid management during tocolysis consisted of 5% dextrose solution at 80 mL/h. Her last prenatal visit on November 14, 2022 (approximately 72 h after initiation of ritodrine therapy), estimated fetal weights of 1700 g and 1600 g for twins A and B, respectively. Shortly after this visit, the patient developed respiratory distress with desaturation, cough productive of pinkish frothy sputum, and dyspnea even with supplemental oxygen at 10 L through simple face mask.

Chest radiography revealed Kerley B lines, peribronchial cuffing, butterfly pattern, and bilateral lower lung pleural effusion suggestive of pulmonary edema [Figure 1]. The treating physician discontinued ritodrine and replaced it with atosiban, maintaining oxygen supplementation at 12 L (oxygen saturation 96%). Fluid administration was restricted to maintenance requirements. Due to persistent respiratory distress, the patient was transferred to our emergency department.

Upon arrival, vital signs showed a temperature of 37°C, pulse of 84 beats per minute, respiratory rate of 20 breaths per minute, blood pressure of 137/63 mmHg, and oxygen saturation of 90% on a nonrebreather mask at 10 L/min. Laboratory studies revealed leukocytosis with neutrophil predominance (white blood cell count 15.2×10^9/L, reference range $4.0–10.0 \times 10^9$/L), microcytic anemia (hemoglobin 7.7 g/dL, reference range 12.0–15.5 g/dL), and elevated NT-proBNP (1178 pg/mL, reference range < 300 pg/mL). No thrombocytopenia or coagulation abnormalities were noted. The electrocardiogram showed sinus tachycardia with bigeminy. Thyroid function tests showed mildly low-free T4 (0.8 ng/dL, reference range 0.9–1.7 ng/dL) and normal thyroid-stimulating hormone (1.2 mIU/L, reference range 0.4–4.0 mIU/L), making thyroid storm unlikely.

POCUS was immediately performed for rapid cardiopulmonary assessment. POCUS showed bilateral diffused B lines in multiple lung fields [Figure 2, representative still image from Video 1], preserved left ventricular (LV) myocardial contractility with an estimated ejection fraction of 60%–65% [Figure 3 and Video 2], no inferior vena cava (IVC) plethora (IVC diameter <2.1 cm with >50% respiratory variation), and no evidence of right ventricle (RV) strain (normal RV/LV ratio < 0.9). These findings were consistent with noncardiogenic pulmonary edema rather than cardiogenic causes, allowing for prompt and targeted management. Tocogram showed no uterine contractions, and fetal heart rates were approximately 120–140 beats per minute for both twins.

Given the patient's compromised respiratory status and the twin gestation at nearly 32 weeks, an emergency cesarean section

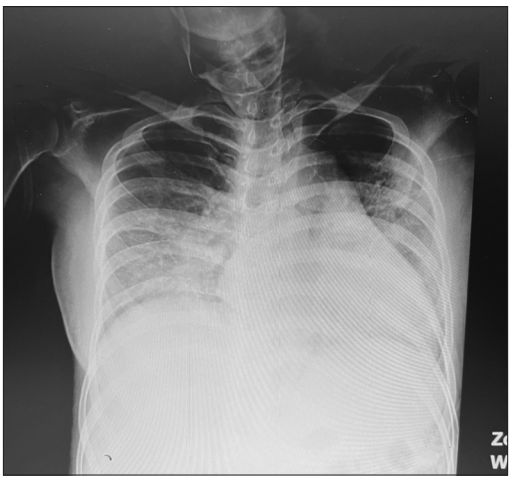

Figure 1: Chest radiograph showing Kerley B lines, peribronchial cuffing, butterfly pattern, and bilateral lower lung pleural effusion consistent with pulmonary edema

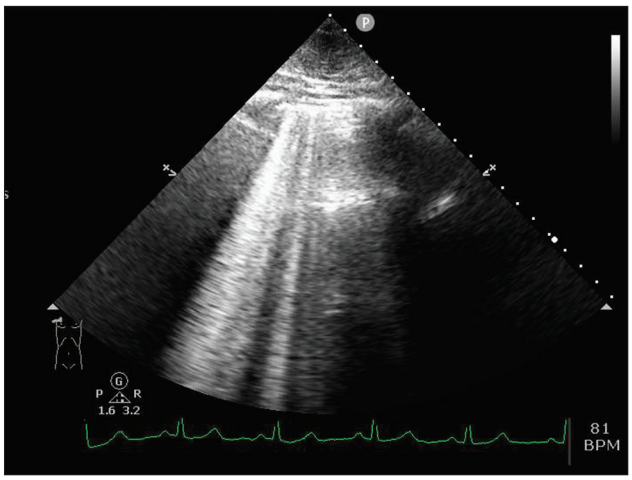

Figure 2: Point-of-care ultrasound image of the lung showing multiple B-lines (comet tail artifacts) consistent with interstitial pulmonary edema

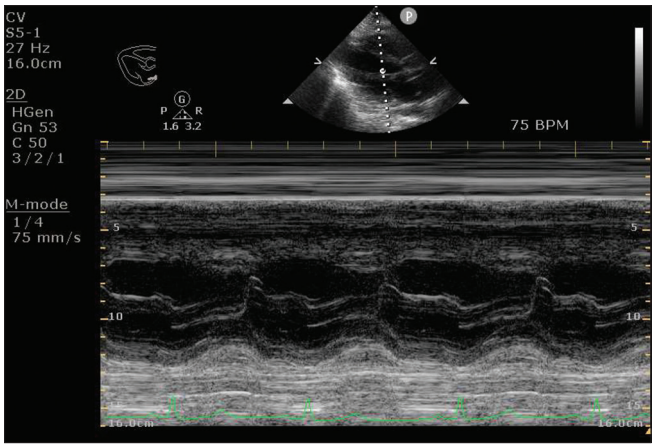

Figure 3: Point-of-care ultrasound revealed EPSS < 7 mm, suggesting preserved left ventricular myocardial contractility

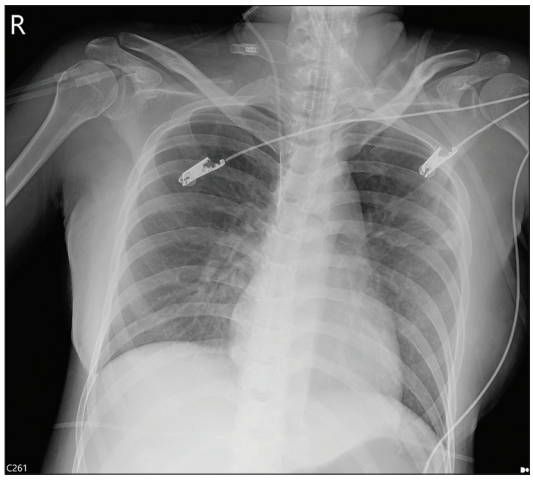

Figure 4: Follow-up chest radiograph after treatment showing resolution of pulmonary edema

was performed on November 14, 2022. Two preterm neonates were delivered: Twin A, a male with vertex presentation weighing 1850 g with Apgar scores of 7 and 8 at 1 and 5 min, respectively; and Twin B, a female with vertex presentation weighing 1798 g with Apgar scores of 7 and 8. Both neonates were transferred to the neonatal intensive care unit, and the mother was admitted to the surgical intensive care unit.

Postoperatively, the patient required intubation and mechanical ventilation. Fluid management was restricted to 60 mL/h. Chest radiography showed improvement in pulmonary edema [Figure 4], allowing for successful extubation after 18 h of mechanical ventilation. The patient was transferred to the general ward on November 15 in stable condition. Postoperative recovery was uneventful. She was discharged home 5 days after admission on November 19, 2022.

Discussion

This case highlights the potential serious pulmonary complications associated with beta-mimetic tocolytic agents, particularly in patients with multiple risk factors. Our patient had several predisposing factors for pulmonary edema, including twin pregnancy, type 1 diabetes mellitus, and hyperthyroidism. The patient's anemia may have also been a contributing factor by decreasing colloid osmotic pressure. The mechanism of ritodrine-induced pulmonary edema is multifactorial. Beta-adrenergic stimulation causes tachycardia and increased cardiac output, which can overwhelm the capacity of the pulmonary circulation.[1,2] According to Lamont, this cardiovascular stress leads to a general vasodilatation resulting in systolic hypotension and a compensatory rise in heart rate, stroke volume, and cardiac output (40%–60% over baseline).[1] Despite a profound decrease in peripheral vascular resistance, mean arterial pressures remain relatively constant due to increased cardiac output. However, with prolonged beta-agonist use, cardiovascular decompensation may occur due to reduced time for left atrial emptying, decreased diastolic ventricular filling, and reduced systolic ejection time, thereby increasing pulmonary capillary hydrostatic pressure.[1]

In addition, beta-mimetics promote significant sodium and water retention through activation of the renin-angiotensin-aldosterone system.[1,3] This increased antidiuretic hormone activity, combined with the activation of the renin-angiotensin system, increases renal sodium resorption.[1] The resultant positive fluid balance due to increased sodium retention has been noted in both primates and humans, with significant decreases in maternal hemoglobin, hematocrit, and serum albumin, therefore reducing plasma colloid osmotic pressure.[1,3] This reduction in colloid osmotic pressure, coupled with increased pulmonary capillary pressure, significantly predisposes to pulmonary edema according to Starling's equation.[2]

The risk is particularly heightened in multiple gestations, where plasma volume expansion is naturally much greater.[1] Twin pregnancies have a 2.5-fold higher risk of developing pulmonary edema with ritodrine compared to singleton pregnancies.[4] These women are theoretically more susceptible to further volume expansion in association with tocolytic infusions, as twin pregnancy is associated with increased levels of urinary aldosterone, which potentially exacerbated by beta-agonists.[2]

The diagnostic approach in this case illustrates the evolving role of bedside ultrasound in obstetric emergencies. While chest radiography and laboratory studies were helpful, POCUS provided immediate additional information that guided management decisions. Computed tomography would have offered higher resolution imaging but at the cost of radiation exposure to the fetuses and potential delay in diagnosis. Formal echocardiography would provide more detailed cardiac assessment but is often not immediately available in emergency settings. The limitations of POCUS include operator dependency and limited ability to assess some aspects of cardiac function in detail, but these are outweighed by its advantages in the acute setting.

POCUS enabled rapid bedside differentiation between cardiogenic and noncardiogenic etiologies, guiding appropriate

clinical decisions. The combination of diffuse bilateral B-lines with preserved LV function, absence of IVC plethora, and no RV strain, findings suggestive of noncardiogenic pulmonary edema, likely due to increased capillary permeability rather than cardiogenic causes such as peripartum cardiomyopathy or fluid overload. This distinction was critical for appropriate management decisions, as emphasized by Lichtenstein's BLUE protocol for lung ultrasound.[5,6]

The utility of POCUS in obstetric emergencies cannot be overstated. Unlike chest radiography, which involves radiation exposure and often requires patient transport, POCUS can be performed immediately at the bedside, providing real-time information to guide clinical decision-making.[7-9] As demonstrated by Volpicelli *et al*. in their international evidence-based recommendations, the identification of multiple B-lines in the anterior lung fields has a sensitivity of 97% and specificity of 95% for interstitial syndrome.[10] Furthermore, the comprehensive cardiopulmonary assessment possible with POCUS – including evaluation of lung fields, cardiac function, and volume status – offers advantages over other diagnostic modalities in emergency situations. In our case, the rapid diagnosis facilitated by POCUS allowed for prompt treatment decisions and likely contributed to the favorable maternal and neonatal outcomes.

The decision to proceed with emergency cesarean delivery rather than continuing tocolysis with an alternative agent was appropriate given the patient's gestational age (nearly 32 weeks) and compromised respiratory status. The temporal relationship between ritodrine administration and the onset of pulmonary symptoms, combined with improvement following discontinuation of the drug and delivery, strongly supports ritodrine as the causative agent. Although hyperthyroidism was initially considered as a contributing factor, subsequent thyroid function tests did not support this diagnosis. This is consistent with findings by Ogunyemi, who identified that preexisting medical conditions can increase the risk of pulmonary edema but are rarely the sole cause in the context of tocolytic therapy.[11]

Current guidelines increasingly recommend alternatives to beta-mimetics for tocolysis, such as calcium channel blockers, oxytocin receptor antagonists, or magnesium sulfate, which have more favorable maternal safety profiles.[11] When beta-mimetics are used, particularly in high-risk patients, close monitoring for early signs of pulmonary edema is essential.

For patients who still receive beta-agonist therapy, we recommend the following monitoring strategies to prevent pulmonary edema:

1. Use of appropriate intravenous fluids (preferably dextrose solutions rather than saline)
2. Strict monitoring of fluid balance with limitation of intake to 1500–2000 mL/24 h
3. Daily weight measurements
4. Regular assessment of vital signs, including oxygen saturation
5. Lower threshold for POCUS assessment in high-risk patients (multiple gestation, diabetes, cardiac, or thyroid disease)
6. Careful attention to medication dosing with the lowest effective dose used for the shortest necessary duration.

Conclusions

Ritodrine-induced noncardiogenic pulmonary edema, while rare, warrants high suspicion in high-risk pregnancies. Early recognition through POCUS – characterized by diffuse B-lines, preserved cardiac function, and absence of venous congestion – enables swift intervention. Given its safety, speed, and bedside availability, POCUS should be routinely employed in the evaluation of respiratory distress in obstetric patients receiving tocolytic therapy.

This case illustrates that judicious use of tocolytics, careful patient selection, and vigilant monitoring are essential to prevent serious complications. Healthcare providers should maintain a low threshold for discontinuing beta-adrenergic tocolytics and implementing alternative management strategies at the first sign of pulmonary complications.

Ethical statement

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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