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Acute Pulmonary Edema Induced by a Low Dose of Ritodrine Hydrochloride: A Case Report

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Objective: Acute pulmonary edema associated with ritodrine hydrochloride is a rare, life-threatening complication, and dose and duration of ritodrine use are closely associated with this pathology. We report a case of acute pulmonary edema associated with short-duration infusion of ritodrine hydrochloride in a patient with pectus excavatum as an underlying factor. **Case Report:** A 30-year-old healthy pregnant woman was treated with oral ritodrine for tocolysis between 31 and 35 weeks of pregnancy. At 36 weeks of gestation, she went into preterm labor, with premature rupture of the membrane and breech presentation, and received an infusion of ritodrine hydrochloride for a few hours. Although she was normotensive until labor onset, mild hypertension and proteinuria were recognized. Intraoperatively, a funnel-chest deformity was observed, and she developed postoperative pulmonary edema associated with dyspnea and wet cough and confirmed on chest radiography and arterial gas analysis, and recovered with supportive care. **Conclusion:** Small-dose infusion of ritodrine hydrochloride might cause pulmonary edema in patients with underlying medical problems, including pectus excavatum.

INTRODUCTION

Acute pulmonary edema during pregnancy has a reported incidence of 0.08% (1), and risk factors include cardiopulmonary diseases, severe preeclampsia, fluid overload, multiple pregnancy, corticosteroid therapy for preterm birth (at 22–28 weeks of gestation), and use of tocolytic agents (1,2). Ritodrine hydrochloride is commonly used for tocolysis in Japan, and one of its most notable adverse effects is acute pulmonary edema, which depends on the dose and duration of the infusion (3,4). We report a case of the illness with somewhat rare risk factors. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CLINICAL CASE

A 30-year-old nulliparous Japanese woman visited our hospital at 7 weeks of singleton gestation with hyperemesis gravidarum during the first trimester of pregnancy. She had no history of cardiopulmonary diseases and smoking nor a remarkable family history, except that her father had hypertension. Physical examination revealed normal findings (height 161 cm); the patient's pre-pregnancy weight was 49 kg, and the nadir of her body weight was 44 kg. She was prescribed oral metoclopramide without hospitalization. Her body weight reverted to the pre-pregnant value at 21 weeks of gestation. She frequently experienced uterine contractions from 31 weeks of gestation and was diagnosed with threatened premature labor based on her symptoms and decreased cervical length, for which she was prescribed oral ritodrine hydrochloride, 5 mg q.i.d. Thereafter, the cervical length remained unchanged, and breech presentation was observed at 35 weeks of gestation. The patient did not opt for extraversion or vaginal delivery, and an elective cesarean section was planned at 38 weeks and 1 day of gestation. No hypertension or proteinuria was detected during the antenatal course. Preoperative blood tests showed normal blood cell count and biochemical parameters. However, preoperative chest radiography revealed a rather high cardiothoracic ratio of 54%, with a left mediastinal shift of the heart (Figure 1). Preoperative electrocardiogram (ECG) showed a negative P wave in lead V1 (Figure 2). She presented with watery discharge and regular uterine contractions at 5:30 am 14 days before the scheduled surgery. Initial examination on admission showed mild uterine contractions at ≥ 5 -min intervals and mild cervical dilation. Normal fetal status was ascertained on cardiotocography, and it was considered feasible to postpone the surgery by a few hours. Intravenous ritodrine hydrochloride was started at a dose of 67 $\mu\text{g}/\text{min}$, at 6:00 am, and increased to 83 $\mu\text{g}/\text{min}$ 70 minutes later because of insufficient tocolysis. The initial infusion rate was a routine for reducing uterine

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activities in our practice despite of a recommendation, 50 $\mu\text{g}/\text{min}$, of the package insert in Japan. The initial dose had not been associated with any problems on safety, as it is rather low in the range of effective dose between 50 and 150 $\mu\text{g}/\text{min}$. She was normotensive (113/62 mmHg), but her urinary sample tested positive for proteinuria (UP/Cr 0.34 g/g $\cdot$ Cr).

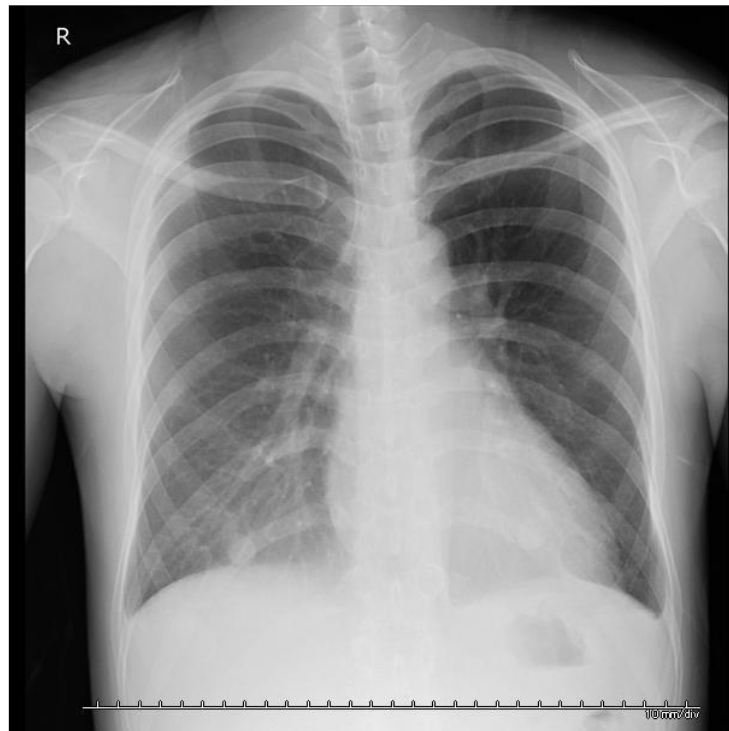


Figure 1. Preoperative chest radiography revealed a rather high cardiothoracic ratio of 54%, with a left mediastinal shift of the heart.

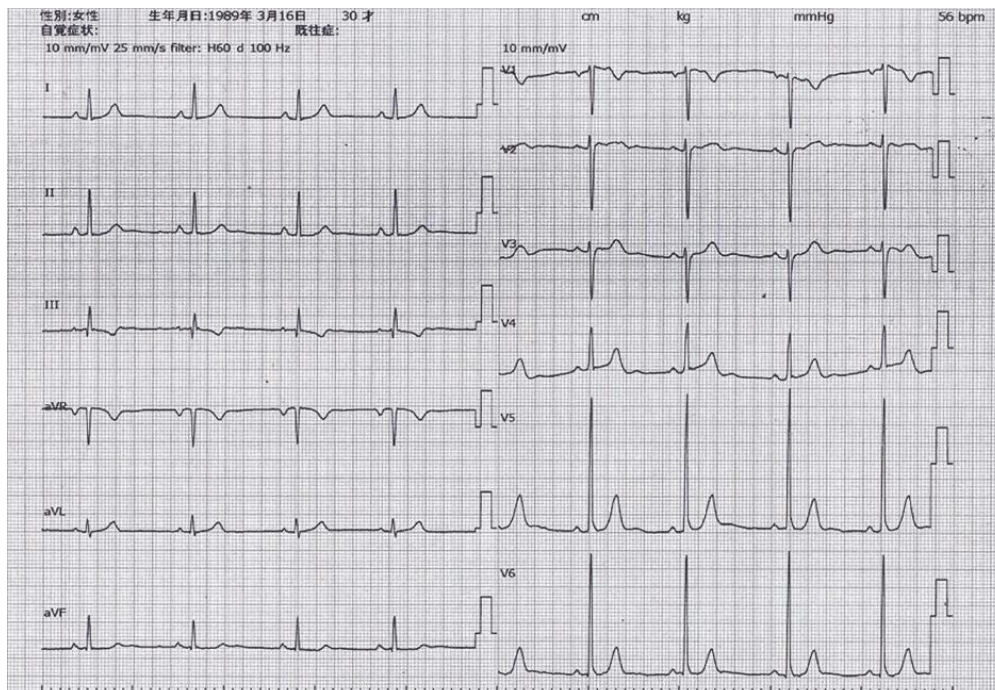


Figure 2. Preoperative electrocardiogram (ECG) showed a negative P wave in lead V1.

After 4 hours of ritodrine infusion, an emergency cesarean section was initiated under spinal anesthesia. Immediately before the spinal tap, the anesthesiologist observed a funnel-chest appearance of the patient in the operation room. However, the surgery was completed uneventfully, and a healthy female baby (weight 2162 g, 5-min Apgar score 9) was delivered. The total pre- and intraoperative volume of infusion was 2000 mL (acetated Ringer's solution 700 mL, 6% hydroxyethyl starch 130/0.4 1300 mL), and the urine output and blood loss were 150 and 610 mL, respectively. The patient's pre- and intraoperative (with a continuous phenylephrine micro-infusion) blood pressure were 144/77 and 130–140/50–70 mmHg, respectively. The operation time was 42 minutes. Postoperatively, she complained of dyspnea, and showed a mild decrease in O₂ saturation (95%) on room air, which subsided on deep breathing before transferring out of the operation room. However, she developed a wet cough and severe dyspnea in the recovery room, with O₂ saturation between 93% and 94%. Supplemental oxygen and a semi-reclining position had only a small effect on the respiratory state. Her PaO₂ was 81 mmHg, and chest radiography showed a butterfly pattern and an increased cardiothoracic ratio of 60% (Figure 3), based on which she was diagnosed with pulmonary edema and transferred to an advanced-care medical institution for intensive cardiopulmonary care. Echocardiography was not performed due to lack of specialist. The dyspnea and wet cough improved rapidly after the transfer without any remarkable treatment, and supplemental oxygen administration was continued until the next day. On echocardiography, her cardiac function was normal, without akinesis of the cardiac wall and no right ventricular failure. On admission, the NT-proBNP level was 205.0 pg/mL. A negative T in Lead III on ECG and elevated troponin T level were observed, but a myocardial infarction was ruled out in the absence of chest pain and normal creatine kinase (CK) levels. She completely recovered and was discharged on the ninth day after hospitalization.



Figure 3. Chest radiography showed a butterfly pattern and an increased cardiothoracic ratio of 60%.

DISCUSSION

This report presents a rare case of pulmonary edema secondary to ritodrine use. Shinohara *et al.* studied the relationship between the incidence of pulmonary edema and total dose of ritodrine hydrochloride for tocolysis in patients with twin pregnancies (5) and found that the total dose was significantly associated with the disease; the most predictable cutoff point for pulmonary edema was 1872 mg. In the present case of a singleton pregnancy without any remarkable history, the patient received a considerably lower dose than the cutoff, although she had been previously treated with oral ritodrine hydrochloride for a long duration before the premature rupture of membranes. Acute pulmonary edema following oral ritodrine administration is extremely rare (6). Furthermore, in this patient, ritodrine hydrochloride was the only tocolytic agent. Previous reports of pulmonary edema associated with ritodrine hydrochloride involved combination use with other tocolytic agents (magnesium sulfate, nifedipine) and/or antenatal corticosteroid therapy (2).

The patient had appeared risk-free for pulmonary edema, and it seemed extremely unlikely that pulmonary edema could be predicted before the infusion of the tocolytic. Retrospectively, there were some problems that could have been recognized before the onset of pulmonary edema. A pectus excavatum was identified preoperatively. Neither a computed tomography (CT) scan nor echocardiography was performed, but preoperative ECG and chest X-ray had shown findings that corresponded to pectus excavatum, which generally include negative P and T waves in V1 on ECG, suggesting aberrant placement of lead V1 due to the dish-like precordia, and a compressed heart (7). Some authors have reported an obscure right heart border and a right-axis shift on chest radiography that are characteristic of severe deformity (8). Pectus excavatum is a congenital anomaly of the chest wall, which occurs approximately in 1 in 400 births. The illness is more common in males than females (9). The effects of pectus excavatum influence not only the cosmetic appearance but also circulatory function, including insufficient cardiopulmonary function, especially during cardiac overload. Stress testing in patients with pectus excavatum can reveal exercise intolerance (10). Pregnancy itself is characterized by volume overload, and the compounding effect of sympathomimetic medication might have caused pulmonary edema in this patient. Furthermore, the total dose of 2000 mL infusion (700 mL crystalloid and 1300 mL colloid) may have been rather excessive for this patient. Preload in an emergency cesarean section is common. Although the patient had no limitation with regard to daily activities, she seemed have a potential risk for cardiac reserve. Second, the patient tested positive for proteinuria on admission. Despite no hypertension, the blood pressure was elevated than earlier. Therefore, she was likely to have had pathophysiology indicative of early-stage preeclampsia, associated with increased capillary permeability, which may lead to edematous conditions. Preoperative precise estimation of her cardiac function could possibly have flagged concerns about ritodrine hydrochloride use.

In conclusion, short-duration low-dose ritodrine hydrochloride use might cause pulmonary edema in patients with underlying medical conditions. Precise estimation of the physiological state of the cardiopulmonary system is desirable in patients who are to undergo tocolysis.

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