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Research article

Atosiban-induced acute pulmonary edema: A rare but severe complication of tocolysis

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ABSTRACT

Background: Atosiban is commonly used to delay premature labor in pregnant women and is thought to have few side effects.

Objectives: To report a case of acute pulmonary edema (APE) following administration of atosiban and conduct a systematic review to identify common characteristics and risk factors of atosiban-associated APE.

Methods: Searches were performed in Pubmed, Embase, and Web of Science using the keyword "Atosiban" combined with the terms "Pulmonary edema" or "Dyspnea" or "Hypoxia" on 9th July 2022. Only case reports of atosiban-associated APE were included without language restrictions. Data were extracted from the reports, and median, range, and percentages were calculated as applicable. The risk of bias was assessed using the Joanna Briggs Institute critical appraisal checklist for case reports.

Results: Seven cases of atosiban-associated APE were included in the systematic review, including our case. APE occurred at a median gestational age of 32 + 6 weeks. Most patients were nulliparous (6/7, 85.7%) and were in multiple pregnancies (5/7, 71.4%). All patients were prescribed antenatal corticosteroids and tocolytics, with three (42.9%) receiving only atosiban and four (57.1%) receiving atosiban and other tocolytics. The median interval from starting atosiban administration to APE onset was about 40 h, and three patients (42.9%) showed symptoms 2–10 h after the end of atosiban treatment. Radiographic examinations (chest X-ray and/or computer tomography scan) confirmed APE in all patients and pleural effusion in four patients (57.1%). Five patients (71.4%) underwent emergency cesarean section, one patient (14.3%) with twin pregnancy had vaginal delivery with the help of suction cup and forceps, and another patient (14.3%) continued the pregnancy. All patients recovered well after administration of oxygen, diuresis, and other supportive therapy.

Conclusion: Atosiban may cause acute pulmonary edema in patients with underlying risk factors. This complication remains rare, but caution during tocolytic treatment using atosiban is recommended.

1. Introduction

Acute pulmonary edema (APE) in pregnancy is an uncommon but life-threatening event with high maternal and perinatal morbidity and mortality [1]. It is characterized by sudden-onset dyspnea and hypoxia secondary to an excess accumulation of fluid in

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the lungs which impairs gas exchange and lung compliance. APE during pregnancy and postpartum period has a reported incidence of 0.08% to 1.5% [2,3]. The most common causes of pulmonary edema in pregnancy have been reported to be the use of tocolytics, underlying cardiac disease, fluid overload, and preeclampsia [4].

Tocolytic agents are commonly used to combat uterine contractions in spontaneous preterm labor to prolong pregnancy, including β-adrenergic agonists, calcium channel blockers (CCBs), prostaglandin synthetase inhibitors, magnesium sulfate and oxytocin receptor antagonists [5]. Atosiban, as a selective oxytocin-vasopressin receptor antagonist, has been reputed as one of the safest tocolytics, with efficacy comparable to other tocolytics [6–11]. Here we report a novel case of APE in a woman treated with atosiban for threatened preterm labor and systematically review cases of atosiban-associated APE to allow full recognition of this serious adverse event of atosiban.

2. Case report

A 32-year-old primigravida was admitted to our hospital with spontaneous preterm premature rupture of the membranes (PPROM) at 27 + 4 weeks of gestation, 18 days after reduction of twin pregnancy to singleton. She had no history of cardiopulmonary diseases. She was conceived through *in vitro* fertilization-embryo transfer (IVF-ET), with two fresh embryos transferred. Sonographic image in the first trimester of pregnancy showed nuchal translucency (NT) thickness of 1.9 and 2.4 mm, respectively. Expanded noninvasive prenatal testing (NIPT-plus) detected an 8.6 Mb duplication of chromosome 15q11.2-q13.3. Ultrasound-guided amniocentesis examination revealed that one fetus had no chromosomal abnormalities, and that the other fetus had 4 copies of chromosome 15q11.2-q13.3, a region covering 26 genes according to Online Mendelian Inheritance in Man (OMIM) and approximately 7640 Kb long. This copy number variant was considered to be pathogenic and might be associated with a wide range of neuropsychiatric disorders. At the request of the patient, intra-amniotic selective fetal reduction was performed with intracardiac injection of potassium chloride to the affected twin at 25 weeks of gestation. Eighteen days after the surgery, the patient was hospitalized for PPROM at 16:26, and successive ultrasound examinations confirmed that it was the surviving fetus that had ruptured membranes.

Physical examination at admission showed a temperature of 36.9 °C, pulse rate of 108 beats per minute (bpm), breath rate of 20 breaths per minute, and blood pressure of 118/81 mm Hg. No uterine contraction was observed, and fetal heart rate (FHR) monitoring of the surviving fetus was normal. Laboratory tests (complete blood count, urine routine, comprehensive metabolic panel, biomarkers of infection, amino-terminal pro-brain natriuretic peptide (NT-proBNP), and cardiac enzymes) results were normal, except for an elevated serum C-reactive protein (CRP) level of 31.9 mg/L and decreased hemoglobin (Hb) level of 81 g/L. Laboratory test results of the patient throughout the disease course were summarized in Table 1.

The patient received four injections of dexamethasone intramuscularly at a dose of 5 mg every 12 h to accelerate fetal lung maturation. She was also given erythromycin (0.25g po q6h) and cefuroxime (0.75g ivgtt q8h) to prevent infection. An hour and a half after admission, she showed uterine contractions every 10–15 min. She was prescribed nifedipine tablets (10 mg po q8h).

On admission day 2, the patient had a low-grade fever with a maximum temperature of 37.6 °C. The white blood cell (WBC) count was 9.91 $\times$ 10^9/L, and serum CRP was 22.2 mg/L. At 17:30, nearly 24 h after starting nifedipine therapy, uterine contractions recurred, lasting 5–10 s every 5–6 min. Nifedipine therapy was discontinued, and atosiban was administered through an infusion pump according to the manufacturer's instructions. Briefly, an induction dose (6.75 mg) of atosiban was administered intravenously for more than 1 min, followed by 18 mg/h for 3 h, and then a maintenance dose of 6 mg/h.

On admission day 3, her temperature fluctuated at 37.2–37.4 °C. The WBC count was 11.91 $\times$ 10^9/L, and serum CRP was 8.0 mg/L.

Table 1
Laboratory test results of our case.

Gestational age	10 + 1 w	17 + 6 w	24 + 5 w (before fetal reduction)	25 + 1 w (after fetal reduction)	27 + 4 w (admission D1)	27 + 5 w (D2)	27 + 6 w (D3)	28 w (before CS)	28 w (after CS)	Normal Range
Hb (g/L)	129	109	88	81	81	81	73	82	85	115–150
WBC ($\times$ 10^9/L)	9.14	10.25	10.18	9.48	7.29	9.91	11.91	16.27	16.34	3.5–9.5
NE (%)	79	83	80	78	79	92	90	86	88	40–75
CRP (mg/L)	ND	13.1	7.9	ND	31.9	22.2	8.0	4.9	15.9	<10
SAA (mg/L)	ND	ND	<3.00	ND	18.64	19.56	10	3.9	55.65	0–10
PCT (ng/mL)	ND	ND	ND	ND	0.24	0.22	0.19	0.19	0.23	<0.5
D-dimer (mg/L)	0.49	3.85	4.43	4.59	ND	ND	ND	5.78	9.74	See below
NT-proBNP (pg/mL)	ND	ND	ND	ND	94.9	ND	ND	ND	2337.0	<96.16
Troponin (ng/mL)	ND	ND	ND	ND	0.012	ND	ND	ND	0.026	<0.034
CK (U/L)	ND	ND	ND	ND	21	ND	ND	ND	74	34–145
CK isoenzyme (U/L)	ND	ND	ND	ND	7	ND	ND	ND	73	<24

Abbreviations: Hb, hemoglobin; WBC, white blood count; NE, neutrophils; CRP, C-reactive protein; NT-proBNP, amino-terminal pro-brain natriuretic peptide; CK, creatine kinase; ND, not done; CS, cesarean section.
The normal range of D-dimer: gestational age <14w: 0–1.55; 14-28w: 0–2.52; ≥28w: 0–4.93.

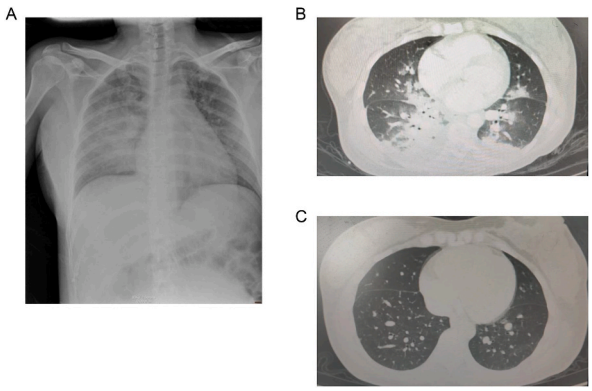

Fig. 1. Chest radiograph of the patient. (A) Supine chest X-ray showed a reduced transparency in the right lung with large patches of high density, and unclear left hilar obscured by the cardiac shadow. (B) Initial computer tomography pulmonary angiograph (CTPA) showed bilateral alveolar pulmonary edema and pleural effusion, without any evidence of pulmonary embolism. (C) A repeated thoracic CT scan showed resolution of pulmonary edema after treatment.

Her cefuroxime therapy was replaced by azobactam sodium/piperacillin sodium (4.5g ivgtt q8h) after a negative penicillin skin test at 14:00.

In the morning of day 4, the patient complained of chest distress. Her temperature was 36.9 °C, blood pressure normal, pulse rate 110 bpm, and transcutaneous oxygen saturation 96%. Oxygen was administered via nasal cannula at a rate of 3 L/min, and her chest distress was relieved. The WBC count was 16.27×10^9/L, and serum CRP was 4.9 mg/L. Despite still in intravenous infusion of atosiban at a dose of 6 mg/h, uterine contractions recurred and became more and more frequent (3-4-min intervals) at 11:00 a.m., and cardiotocography showed the baseline FHR was 165 bpm. Chorioamnionitis and acute fetal distress were suspected, and an emergency cesarean section (CS) was going to be performed.

On the way to the operation room, the patient suddenly presented with dyspnea and hypoxia. Her temperature and blood pressure were normal, pulse rate 110 bpm, and respiratory rate 28 breaths per minute. Oxygen saturation was 85–90% on room air and 98–99% under oxygen therapy at 10 L/min through a mask. When asked about the medical history, the patient complained that she had chest discomfort and nonproductive cough last night, without orthopnea. Arterial blood gas analysis under oxygen therapy showed PaO2 157 mmHg, PaCO2 33.7 mmHg, and pH 7.421. Bedside electrocardiogram (ECG) revealed a sinus tachycardia without any evidence of arrhythmia or myocardial infarction. Supine chest X-ray (Fig. 1A) revealed a reduced transparency in the right lung with large patches of high density, suggesting possible right pneumonia, and further computer tomography (CT) examination was recommended. At 14:47, a dead female and a live female neonate (height: 36 cm; weight: 1190g; Apgar score at 1 and 5 min: 9 and 9, respectively) were delivered by successful CS under spinal anesthesia. Umbilical arterial blood gas analysis revealed pH 7.330 and base excess extracellular fluid (BEecf) −1 mmol/L. The live baby was transferred to neonatal intensive care unit. The patient remained in a critical state with hypoxia requiring continuous oxygen inhalation through a mask. An urgent consultation request was sent to Renji Hospital, School of Medicine, Shanghai Jiaotong University, a comprehensive large-scale tertiary hospital. Postoperative blood tests disclosed a WBC count of 16.34×10^9/L, Hb of 85 g/L, D-dimer of 9.74 mg/L, CRP level of 15.9 mg/L, NT-proBNP of 2337.0 pg/mL (normal range: <96.16 pg/mL), troponin of 0.026 ng/mL, creatine kinase of 74 U/L, and creatine kinase isoenzyme of 73 U/L. Hepatorenal function and electrolyte results were normal, and infection screening revealed no positive results. The patient was treated with tazobactam sodium/piperacillin sodium, azithromycin and ambroxol. At 19:45, the consulting doctor from Renji Hospital arrived. Physical examination revealed no wet rales in bilateral lungs, or any edema, swelling, skin color changes or tenderness in upper and lower extremities. The patient was suspected of having pulmonary embolism. As suggested by the consulting doctor, the patient was treated with low molecular weight heparin and transferred to Renji Hospital for further examination and treatment immediately.

In Renji hospital, Computer tomography pulmonary angiograph (CTPA) showed bilateral alveolar pulmonary edema and pleural effusion, without any evidence of pulmonary embolism (Fig. 1B). Serum D-dimer was 3.45 mg/L and BNP was 438 pg/mL (normal range: 0–100 pg/mL). Echocardiography and venous duplex Doppler ultrasonographic examination results were normal. She was given anti-infective, anticoagulation, diuretic, and supportive treatment. Seven days later, the patient's discomfort was relieved. A repeated laboratory test showed WBC count of 6.9×10^9/L, Hb of 103 g/L, D-dimer of 0.55 mg/L, CRP of 2.95 mg/L, and BNP of 18 pg/mL. A repeated CT scan of the thorax day 7 postpartum (Fig. 1C) revealed substantial resolution of the pulmonary edema, and she was discharged home day 12 postpartum.

The patient had read the information about the case report and voluntarily consented to publish her story with a written informed consent.

3. Methods

3.1. Search strategy and selection criteria

This systematic review was registered with the International Prospective Register of Systematic Reviews (Registration number: CRD42022373793). A search of Pubmed, Embase, and Web of Science was conducted using the keyword "Atosiban" in combination with the terms "Pulmonary edema" or "Dyspnea" or "Hypoxia" from the database inception until 9th July 2022. There was no restriction of language to allow collection of as many cases as possible. In addition, the references of the retrieved articles were manually screened to identify relevant manuscripts not in the database. After removing duplicate articles, relevant articles were selected first by title and abstract and then by full text of the remaining articles. Only case reports and case series of atosiban-associated pulmonary edema in pregnancy were included. Cases of pulmonary edema with definite other causes were excluded.

3.2. Assessment of data quality and risk of bias

The search was performed by two independent authors (Yang ZW and Wu W) in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [12]. Two authors (Yang ZW and Yu Y) evaluated independently the data quality and risk of bias of the final selected studies using the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports and case series [13]. Disagreement was solved by reevaluation and discussion with a more experienced author (Liu HY).

3.3. Data extraction and synthesis

For each case, available data regarding maternal demographic characteristics, duration of atosiban treatment, interval from starting using atosiban to symptoms onset, clinical presentations, relevant examination results, treatment, delivery characteristics, and maternal and perinatal outcomes were extracted independently from the reports by two authors. Maternal demographic characteristics included age, gestational age, parity, medical history, and number of fetuses in the uterus. Data were then cross-checked, and any discrepancies were solved by discussion with a third author. A narrative synthesis was conducted with detailed description of each individual case. Median and range were calculated for continuous data, and frequency and percentages for categorical data.

4. Results

4.1. Study selection and characteristics

The search yielded 27 abstracts from Pubmed, 17 abstracts from Embase, and 28 abstracts from Web of Science. A total of 56 publications were obtained after removing duplicates. Titles and abstract screening excluded 49 irrelevant papers. Full-text examination excluded one article because the patient did not develop APE [14]. Finally, 6 cases from 6 articles were included in this systematic review in addition to our novel case for a total of 7 cases. A flowchart of the systematic review is shown in Fig. 2.

4.2. Risk of bias of included studies

The risk of bias was assessed using the JBI critical appraisal tool for case report (Supplementary Table 1). Overall, the quality of the included articles was acceptable. The risk of bias was judged to be low for description of patient demographic characteristics, diagnosis, treatment and maternal outcomes in all cases. Perinatal outcomes had the highest risk of bias and were not described in two cases [15,16].

4.3. Synthesis of results

A total of 7 patients including our patient were included in the systematic review. Characteristics of the seven reported cases are presented in Table 2. All the cases were from Europe (6/7, 85.7%) except our case. The median age of the patients was 32 (Range: 25–43) years. APE occurred at a median gestational age of 32 + 6 (Range: 28–34 + 4) weeks. Six patients (85.7%) were nulliparous and one (14.3%) primiparous. Five patients (83.3%) referred to hospital because of premature labor and two (28.6%) because of PPROM. Four patients (66.7%) were in multiple pregnancies, two (28.6%) in singleton pregnancy, and our patient in twin pregnancy reduced to singleton. All the patients reported no history of cardiopulmonary disease except that one patient had an asthma history and smoked 10 cigarettes a day [15]. All the patients (100%) were prescribed antenatal corticosteroids and tocolytics. Three patients (42.9%) received only atosiban [15,17,18], three (42.9%) received CCBs at first and then switched to atosiban [16,19], and one patient (14.3%) received atosiban, indomethacin and micronized progesterone at the same time [20]. The median duration of atosiban treatment was about 40 (Range: 10–72) hours. The median interval from starting atosiban administration to APE symptoms onset was about 40 (Range: 12–72) hours. Of note, three patients (42.9%) presented with APE symptoms 2–10 h after the end of atosiban treatment [15, 18]. The most common presentations were dyspnea, hypoxia and tachypnea.

The diagnosis, treatment and maternal outcomes of the cases were shown in Table 3. Laboratory tests showed that two patients (28.6%) including ours had mild anemia [15]. Four patients (57.1%) reported NT-proBNP or BNP levels [16,17,19], and three patients showed elevated NT-proBNP or BNP levels [16,19]. Electrocardiogram examination was normal in all patients except two with

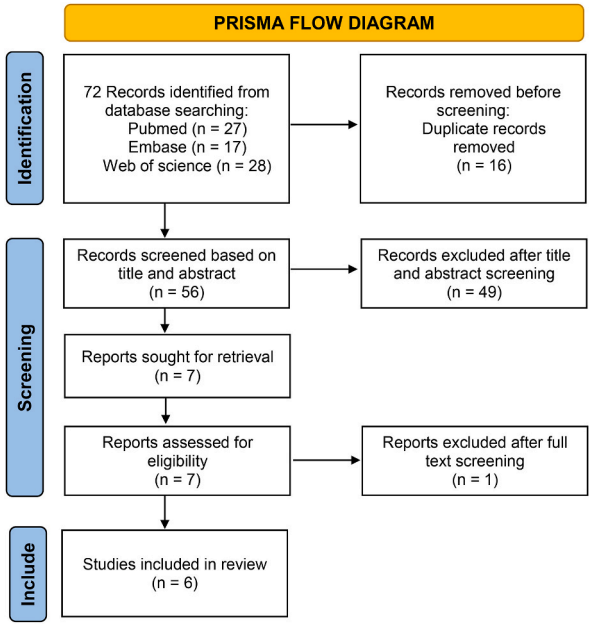

Fig. 2. The flowchart of the systematic review.

tachycardia [17]. Echocardiography examination was normal in all patients except that one patient had a left ventricular ejection fraction (LVEF) of 45% [19]. Radiographic Examination (chest X-ray and/or CT scan) confirmed acute pulmonary edema in all the patients (100%) and pleural effusion in four patients (57.1%). Three patients (42.9%) were transferred to the intensive care unit [16,19,20]. Six patients (85.7%) were administered oxygen therapy, of whom three (50%) underwent noninvasive ventilation [17–19], two (33.3%) were intubated and ventilated [16,20], and one patient (16.7%) underwent continuous positive airway pressure (CPAP). All patients (100%) received furosemide therapy. Three patients (42.9%) also received anti-infective therapy [19,20]. Five patients (71.4%) underwent emergency CS [15–17,20], one patient (14.3%) with twin pregnancy had a vaginal delivery with the help of suction cup and forceps [19], and another patient (14.3%) continued the pregnancy [18]. The median gestational age at delivery was 33 + 3 weeks (Table 4). Median Apgar score at 1min, 5min, and 10min was 6.5, 8.5, and 9, respectively (Table 4). All patients recovered well and discharged home about 1–12 days after effective treatment. No maternal or fetal mortality was reported.

5. Discussion

In this study, we reported a rare case of acute pulmonary edema in a 32-year-old primigravida after administration of atosiban, and conducted a systematic review of atosiban-associated APE cases. To the best of our knowledge, this is the first systematic review of atosiban-related APE. We summarized the clinical characteristics of these cases at length, proposed possible risk factors contributing to APE, and highlighted increased vigilance when using atosiban as a tocolytic.

APE is one of many serious complications associated with the use of tocolytics, such as β-adrenergic agonists [21,22] and calcium channel antagonists [23], but has rarely been reported with atosiban. Atosiban was developed by the Swedish company Ferring Pharmaceuticals for the delay of threatened preterm labor in pregnant adult women and first reported in the literature in 1985 [24]. A few prospective, randomized clinical trials [25–28] have demonstrated that atosiban is effective in diminishing uterine contractions in women with threatened preterm birth without causing significant maternal, fetal, or neonatal adverse effects. Although commonly used in Europe, China and Korea, atosiban is not approved for use as a tocolytic in the United States and Japan due to concerns about the drug's efficacy and safety [29].

This systematic review has revealed that there are only 7 case reports of atosiban-associated APE including this case. Six out of 7 (85.7%) patients were nulliparas, suggesting nulliparity was a potential risk factor. Consistent with our finding, Keepanasseril *et al.* found nulliparity was a significant risk factor of pulmonary edema in 55 pregnant women with preeclampsia [30]. Five out of 7 patients were multifetal pregnant including our patient, who was in twin pregnancy reduced to singleton, to be more precise. APE in the patients occurred between 28 and 34 + 4 weeks of gestational age with a median of 32 + 6 weeks. It is reported that maternal blood volume increases progressively from 6 to 8 weeks of gestation until 30–34 weeks and then plateaus until delivery [31]; therefore it seems reasonable that gestational age of 30 to 34 week was a risk factor. In our case, the patient developed APE at as early as 28 weeks of pregnancy, probably due to the combination of twin pregnancy reduced to singleton, PPROM, moderate anemia, and tachycardia.

Corticosteroid, which could lead to the retention of water and sodium [32], was administered in all the patients in this systematic review, suggesting antenatal corticosteroid therapy might be a risk factor, consistent with prior reports [23,33]. Interestingly, it is reported that corticosteroid was not a risk factor for APE when used alone, but was when combined with tocolytic agents [34]. The

Table 2
Characteristics of the reported cases of acute pulmonary edema associated with atosiban therapy.

Study	Country	Age (years)	Gestational age at admission (weeks)	Parity	Pregnancy	Medical history	Reason for referral	Corticosteroid therapy	Tocolytics	Duration of atosiban treatment (hours)	Interval from starting using atosiban to APE onset (hours)	Gestational age at APE (weeks)	Presenting symptoms
Donders *et al.*, 2008 [20]	Belgium	33	32 + 4	0	Singleton	NA	Preterm labor	Yes	Atosiban + progesterone + Indomethacin	56–72	56–72	32 + 6	Nasal congestion, hot flushes, dyspnea, cyanosis, orthopnea
Perbet *et al.*, 2008 [19]	France	31	34	1	Twin	No	Preterm labor	Yes	Nifedipine → Nicardipine → Atosiban	10	12	About 34 + 4	Hypoxia, fever, tachypnea
Fernández *et al.* 2011 [17]	Spain	33	30	0	Twin	NA	Preterm labor	Yes	Atosiban	36–48	36–48	30 + 1	Nasal congestion, dyspnea, tachypnea, orthopnea, cyanosis
Seinen *et al.*, 2013 [15]	Netherlands	32	33 + 3	0	Triplet	Asthma; Smoke 10 cigarettes a day	Preterm labor	Yes	Atosiban	48	60	33 + 5	Shortness of breath, chest pain
Hourbracq *et al.*, 2017 [18]	France	25	30	0	Twin	NA	Preterm labor	Yes	Atosiban	48	56	30 + 2	Dyspnea, hypoxia
HARDY *et al.*, 2019 [16]	Belgium	43	34	0	Singleton	Hypothyroidism, treated with levothyroxine; Anemia	PPROM	Yes	D1: Nifedipine D2: Nifedipine + Atosiban	<24	<24	34 + 1	Dyspnea, hypoxia, tachycardia
Our study	China	32	27 + 4	0	Twin reduced to singleton	Anemia	PPROM	Yes	Nifedipine→ Atosiban	40	40	28	Dyspnea, hypoxia, tachypnea, tachycardia

(*continued on next page*)

Table 2 (*continued*)

Study	Country	Age (years)	Gestational age at admission (weeks)	Parity	Pregnancy	Medical history	Reason for referral	Corticosteroid therapy	Tocolytics	Duration of atosiban treatment (hours)	Interval from starting using atosiban to APE onset (hours)	Gestational age at APE (weeks)	Presenting symptoms
Total	Belgium: 2/7 (28.6%)	32 (25–43)	32 + 4 (27 + 4–34)	0: 6/7 (85.7%)	Singleton: 2/7 (28.6%)	NA: 3/7 (42.9%)	Preterm labor: 5/7 (71.4%)	Yes: 7/7 (100%)	Atosiban: 3/7 (42.9%)	40 (10–72)	40 (12, 72)	32 + 6 (28, 34 + 4)	Dyspnea: 7/7 (100%)
	France: 2/7 (28.6%)			1: 1/7 (14.3%)	Multiple: 4/7 (57.1%)	Anemia: 2/7 (28.6%)	PPROM: 2/7 (28.6%)		Atosiban & CCBs: 3/7 (42.9%)				Hypoxia: 6/7 (85.7%)
	Spain: 1/7 (14.3%)				Twin reduced to singleton: 1/7 (14.3%)	Asthma and Smoke: 1/7 (14.3%)			Atosiban & Progesteron & Indomethacin: 1/7 (14.3%)				Tachypnea: 3/7 (42.9%)
	Netherlands: 1/7 (14.3%) China: 1/7 (14.3%)					Hypothyroidism: 1/7 (14.3%)							Cyanosis: 2/7 (28.6%) Orthopnea: 2/7 (28.6%) Tachycardia: 2/7 (28.6%) Nasal congestion: 2/7 (28.6%) Hot flushes: 1/7 (14.3%) Chest pain: 1/7 (14.3%) Fever: 1/7 (14.3%)

Abbreviations: APE, acute pulmonary edema; PPROM, preterm premature rupture of the membranes; CCBs: calcium channel blockers; NA, not available.
→ denotes be replaced with; & denotes and.

Table 3
Diagnosis, treatment, and maternal outcomes of atosiban-associated acute pulmonary edema cases.

Study	Infection screen	Electrocardiogram	Echocardiogaphy	Sonography of lower limb vessels	Radiographic examinations		Fetal cardiotocography	Treatment	Delivery	Maternal outcomes
					Chest X-ray	CT scan				
Donders *et al.*, 2008 [20]	NA	Normal	Normal	Normal	Bilateral "butterfly-like'' alveolar diffusion, without pleural effusion or cardiac enlargement	No signs of PE	Normal	ICU admission; Intubation and ventilation; Furosemide; LMWH; Antibiotics; 2 U of red blood cell transfusion	Emergency CS	Discharged 10 days postpartum
Perbet *et al.*, 2008 [19]	Negative	Normal	LVEF: 45%	NA	Bilateral alveolar diffusion predominantly on the left	Bilateral nodular opacities sparing the right upper lung lobe, moderate left-predominant pleural effusions	NA	ICU admission; NIV; Furosemide; Antibiotics; Drain pleural effusions; Perindopril	Vaginal delivery with the help of suction cup forceps	Discharged on D9; Echocardiogaphy was fully recovered 30 days postpartum
Fernández *et al.* 2011 [17]	Negative	Tachycardia	Normal	Normal	Bilateral 'butterfly-like' alveolar diffusion without pleural effusion or cardiac enlargement	NA	Normal	CPAP; Furosemide	Emergency CS	Achieving clinical and radiological recovery within 24 h
Seinen *et al.*, 2013 [15]	NA	Normal	Normal	NA	Enhanced pulmonary vascular drawing with basal bilateral pleural effusion	NA	NA	Furosemide; Fluid balance	Emergency CS	Discharged 4 days postpartum
Hourbracq *et al.*, 2017 [18]	NA	Normal	Normal	NA	Bilateral alveolar diffusion without pleural effusion, cardiac enlargement, or any sign of infection	NA	Normal	NIV; Furosemide	Continue the pregnancy	Discharged on D6
HARDY *et al.*, 2019 [16]	Negative	Normal	Normal	NA	Fluid overload as well as pleural effusions	Pleural effusions as well as ground glass images, evoking APE	Episodes of bradycardia	ICU admission; Intubation and ventilation; Fluid balance; Furosemide	Emergency CS	Extubated on the 2nd day and returned to the maternity ward on the 3rd day
Our study	Negative	Tachycardia	Normal	Normal	Reduced transparency in the right lung with large patches of high density, suggesting possible right pneumonia	Bilateral alveolar pulmonary edema and pleural effusion, without evidence of PE	Tachycardia	NIV; Furosemide; LMWH; Antibiotics; Fluid balance	Emergency CS	Discharged 12 days postpartum

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Table 3 (*continued*)

Study	Infection screen	Electrocardiogram	Echocardiogaphy	Sonography of lower limb vessels	Radiographic examinations		Fetal cardiotocography	Treatment	Delivery	Maternal outcomes
					Chest X-ray	CT scan				
Total	Negative: 4/7 (57.1%)	Normal: 5/7 (71.4%)	Normal: 6/7 (85.7%)	NA: 4/7 (57.1%)	Bilateral alveolar edema: 6/7 (85.7%)		Normal: 3/7 (42.9%)	Oxygen: NIV 3/7 (42.9%); Intubation and ventilation 2/7 (28.6%); CPAP 1/7 (14.3%); NA 1/7 (14.3%)	Emergency CS: 5/7 (71.4%)	
	NA: 3/7 (42.9%)	Tachycardia: 2/7 (28.6%)	Abnormal: 1/7 (14.3%)	Normal: 3/7 (42.9%)	Enhanced pulmonary vascular drawing: 1/7 (14.3%)		NA: 2/7 (28.6%)	Furosemide: 7/7 (100%)	Vaginal delivery: 1/7 (14.3%)	
					With pleural effusion: 4/7 (57.1%)		Bradycardia: 1/7 (14.3%)	ICU admission: 3/7 (42.9%)	Continue the pregnancy: 1/7 (14.3%)	
					Without pleural effusion: 3/7 (42.9%)		Tachycardia: 1/7 (14.3%)	Fluid balance: 3/7 (42.9%) Antibiotics: 3/7 (42.9%) LMWH: 2/7 (28.6%) Drain pleural effusions: 1/7 (14.3%) blood transfusion: 1/7 (14.3%) Perindopril: 1/7 (14.3%)		

Abbreviations: NIV: non-invasive ventilation; CPAP, continuous positive airway pressure; NA, not available; CS, cesarean section; CT: computer tomography; PE: pulmonary embolism; ICU: intensive care unit; LMWH: low-molecular-weight heparin.

Table 4
Perinatal outcomes of atosiban-associated acute pulmonary edema cases.

Study	Gestational age at birth (weeks)	Sex	Birthweight (g)	Apgar score at 1 min	Apgar score at 5 min	Apgar score at 10 min	Neonatal Complications
Donders *et al.*, 2008 [20]	33	male	1990	7	8	9	No
Perbet *et al.*, 2008 [19]	About 34 + 5	NA	NA	First twin: 7 Second twin: 6	First twin: 8 Second twin: 8	First twin: 8 Second twin: 9	NA
Fernández *et al.* 2011 [17]	About 30 + 1	NA	NA	First twin: 6 Second twin: 6	NA	First twin:10 Second twin: 9	NA
Seinen *et al.*, 2013 [15]	33 + 6	NA	Normal	NA	NA	NA	No
HARDY *et al.*, 2019 [16]	About 34 + 1	NA	NA	NA	NA	NA	NA
Our study	28	Female	1190	9	9	10	No
Total	33 + 3	NA: 4/6 (66.7%) Male: 1/6 (16.7%) Female: 1/6 (16.7%)		6.5 (6–9)	8.5 (8–9)	9 (8–10)	No: 3/6 (50%) NA: 3/6 (50%)

Abbreviations: NA, not available.

patients showed signs of APE about 10–72 h after starting atosiban therapy, and three patients developed APE about 2–10 h after the end of atosiban treatment. This time window is of great significance, reminding us to pay attention to maternal respiratory symptoms, even after ending atosiban treatment.

In this systematic review, four patients including ours received additional tocolytic agents, predominantly CCBs. These concomitant tocolytics could not be excluded as a possible cofactor related to APE. Although the patients reported by Sébastien Perbet [19] and Hardy PY [16] developed symptoms of APE after administration of atosiban, APE was attributed by the authors to CCBs, which were used before or in combination with atosiban. Atosiban has long been reputed as one of the safest tocolytics. However, the side effects of atosiban may have been underestimated. Serious adverse events during atosiban treatment have not been reported in several large cohort studies [28,35,36], nevertheless, it should be noted that the majority of the patients enrolled in the studies were in singleton pregnancies and received only atosiban treatment, which may not fully reflect real-world data. Moreover, several randomised controlled trials (RCTs) [14,28,36,37] reported respiratory symptoms such as shortness of breath and dyspnea in women receiving atosiban therapy, suggesting atosiban may have adverse effects on maternal respiratory system. Furthermore, several cases of APE during atosiban therapy have been reported in prospective cohort studies, despite atosiban were used together with other tocolytics [7, 37]. Combined with these scattered case reports of atosiban-associated APE [15–20], maybe it is time to update our understanding of the side effects of atosiban.

The pathophysiology of APE during tocolytic treatment using atosiban remains unclear. Maternal physiologic cardiopulmonary adaptations during pregnancy such as an increased maternal blood volume, cardiac output and oxygen consumption, predispose a pregnant women to developing APE [2]. On the other hand, it is reported that oxytocin has a protective effect in acute lung injury, cardiac ischemia, and cardiomyopathies acting through oxytocin receptors (OXTRs) and vasopressin V1A receptors (V1ARs) [38–40]. As an oxytocin–vasopressin receptor antagonist that competitively inhibits oxytocin from binding to its receptors, atosiban has been reported to abolish the cardiopulmonary protective effect of oxytocin in *in vitro* and *in vivo* studies [41–43]. This pharmacological effect of atosiban may predispose a pregnant woman to the development of acute lung injury and APE, especially when combined with other risk factors, such as spontaneous premature labor, multifetal pregnancy, nulliparity, gestational age of 30 to 34 weeks, underlying cardiovascular diseases, concurrent corticosteroid therapy and use in combination with other tocolytics. Of course, further investigations are warranted to elucidate the underlying mechanisms.

Treatment of atosiban-induced APE includes discontinuation of atosiban and a symptomatic and supportive treatment such as oxygen therapy and diuretics. As illustrated in this systematic review, NIV and CPAP can be an alternative ventilatory treatment, avoiding the use of intubation and mechanical ventilation. After prompt and effective treatment, all the patients made a full recovery, and no maternal or perinatal mortality were reported.

CCBs were first reported as tocolytics in 1972 [44], while the first case of CCBs-associated APE was not reported until 2006 [45], which aroused attention and subsequently more and more CCBs-associated APE cases [23,46–48] were reported. Similarly, though further studies are warranted to evaluate a causal association between atosiban administration and the development of APE, this study is supposed to draw attention to the possible side effects of atosiban and highlight vigilance during the treatment of atosiban.

The main limitation of this study was that all the included studies were case reports, without control group. Next, the number of cases included in this systematic was limited. Last but not least, the causal relationship between atosiban and APE needs to be verified, and mechanism study is warranted.

6. Conclusions

Atosiban may cause APE in women with underlying risk factors. This complication remains rare, but caution during the use of

atosiban as a tocolytic is recommended, especially in patients with possible risk factors, such as spontaneous premature labor, fetal lung maturation corticosteroid therapy, multifetal pregnancy, nulliparity, gestational age of 30 to 34 weeks, underlying cardiovascular diseases, and concomitant use of other tocolytics.

PROSPERO registration

This systematic review was registered with the International prospective Register of Systematic Reviews (Registration number: CRD42022373793) on 18th November 2022

Author contribution statement

Zuwei Yang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Wei Wu and Yi Yu: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Haiyan Liu: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15829.

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