Complications of lymphangioleiomyomatosis in pregnancy: a case report and review of the literature

Check for updates

Eileen Wang-Koehler, MD; Adina R. Kern-Goldberger, MD, MPH, MSCE; Sindhu K. Srinivas, MD, MSCE

Lymphangioleiomyomatosis is a rare cystic lung disease primarily affecting premenopausal females and may be exacerbated by pregnancy. We conducted a literature review of lymphangioleiomyomatosis during pregnancy with a specific focus on related maternal morbidity and obstetrical outcomes. We also report a case of lymphangioleiomyomatosis that presented as an acute spontaneous pneumothorax in the third trimester of pregnancy, followed by significant maternal morbidity. A 37-year-old primigravid woman who presented at 29 weeks 5 days gestation with chest pain was diagnosed with spontaneous pneumothorax. Further imaging demonstrated cystic lung lesions and renal angiomyolipomas. She developed severe abdominal pain concerning for placental abruption that led to an urgent cesarean delivery at 30 weeks 2 days gestation. Her course was complicated by recurrent pneumothorax, superimposed preeclampsia, and significant ileus and bowel dilation complicated by bowel perforation. For patients with a clinical suspicion of lymphangioleiomyomatosis in pregnancy, prompt recognition, diagnosis, and referral to appropriate multidisciplinary subspecialists is critical to mitigate complications and optimize outcomes both during and after pregnancy.

Key words: bowel perforation, case reports, cystic lung lesions, literature review, maternal morbidity, pregnancy, pulmonary complications, renal angiomyolipomas, renal complications

Introduction

Lymphangioleiomyomatosis (LAM) is a rare cystic lung disease characterized by the proliferation of smooth muscle cells in the lungs. It is associated with a mutation in the tuberous sclerosis gene (TSC2) and inappropriate activation of mammalian target of rapamycin (mTOR) signaling, which regulates cellular growth. LAM can be isolated and sporadic or associated with tuberous sclerosis, which is an autosomal dominant genetic disorder involving seizures, cognitive impairment, and tumors, especially in the brain. LAM is characterized by proliferation of smooth muscle cells in the lungs, leading to characteristic thin-walled cysts, or blebs, and causing an obstructive pattern of lung disease. It can also affect other organ systems, including the kidneys and lymphatics.[1] Renal angiomyolipomas (AMLs), which are benign tumors containing smooth muscle, blood vessels, and adipose tissue, are found in up to 30% of patients with sporadic LAM and may cause acute bleeding. Other manifestations include chylous effusions and lymphadenopathy. Diagnosis of LAM is primarily based on radiology findings, although lung biopsy is the gold standard. Elevated vascular endothelial growth factor D (VEGF-D) levels, secreted by LAM cells in the lung, can also support the diagnosis.[2]

LAM primarily affects premenopausal females, and estrogen plays a significant role in its pathogenesis.[1] Pregnancy and the use of estrogen-containing contraceptives can exacerbate the symptoms of patients with LAM. We report a case of LAM that presented as an acute, spontaneous pneumothorax in the third trimester of pregnancy and that was followed by significant peridelivery maternal morbidity. Informed consent for publication of this case report was obtained from the patient. We also conducted a systematic literature review on LAM during pregnancy with specific focus on maternal morbidity, clinical course, and obstetrical outcomes that ultimately encompassed 24 case reports and 5 observational studies.

Case

A 37-year-old primigravid patient at 29 weeks 5 days gestational age initially presented with 2 days of right-sided chest pain. Her only significant past medical history was mild chronic hypertension. She denied dyspnea, cough, edema, fevers, and rashes. A computed tomography (CT) angiography of the chest to rule out a pulmonary embolism demonstrated a right-sided pneumothorax measuring 2.2 cm and at least 20 thin-walled cysts (blebs) ranging from 0.5 to 1 cm in diameter (Figure 1). There were also 3 subcentimeter exophytic left renal hyperattenuating lesions, concerning for hemorrhagic cysts. A right chest tube was placed to relieve the pneumothorax, suspected to be secondary to ruptured blebs. The patient received betamethasone for fetal

From the Department of Obstetrics and Gynecology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA (Drs Wang-Koehler and Srinivas); Division of Maternal-Fetal Medicine, Women's Health Institute, Cleveland Clinic Foundation, Cleveland, OH (Dr Kern-Goldberger); Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA (Dr Srinivas)

The authors report no conflict of interest.

This study did not receive any funding.

Written consent was obtained from the patient featured in this case report.

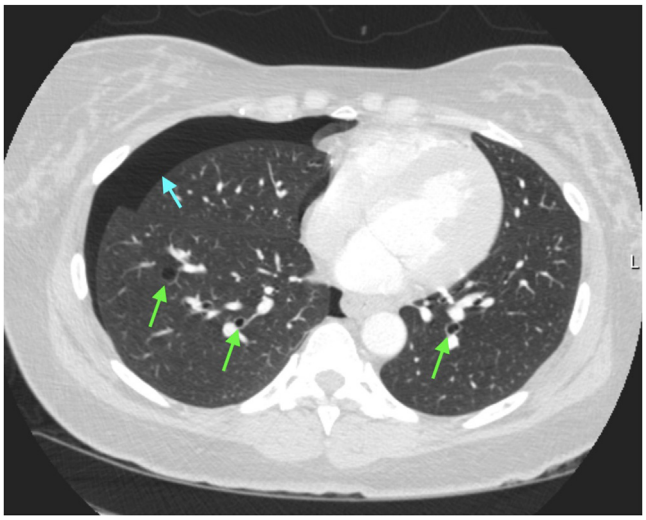
Corresponding author: Eileen Wang-Koehler, MD. Eileen.Wang-Koehler@pennmedicine.upenn.edu

2666-5778/$36.00

© 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

http://dx.doi.org/10.1016/j.xagr.2024.100309

FIGURE 1
Computed tomography scan of chest



Blue arrow indicates a pneumothorax; green arrows indicate cystic lesions.

Wang-Koehler. Lymphangioleiomyomatosis in pregnancy. Am J Obstet Gynecol Glob Rep 2024.

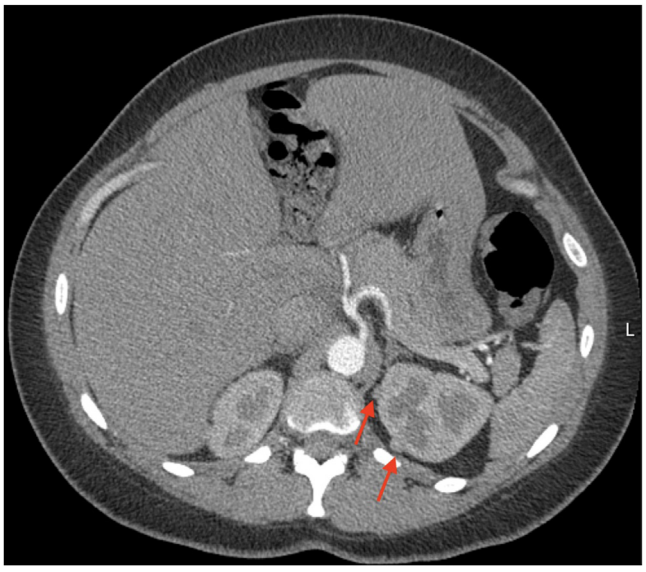
lung maturity and magnesium for fetal neuroprotection and was then transferred to our facility for a higher level of care for these findings and also because of new severe-range blood pressures concerning for superimposed preeclampsia.

Upon arrival at our hospital, the patient was in significant pain at the chest tube site and required a hydromorphone patient-controlled analgesia (PCA) pump. The patient had several severe-range blood pressure measurements necessitating multiple doses of intravenous labetalol, as well as proteinuria (urine protein/creatinine ratio of 0.4) but without preeclampsia symptoms or abnormalities in the platelet counts or creatinine or transaminase levels. The interventional pulmonology division was consulted with a working diagnosis of a primary spontaneous pneumothorax. The chest tube was removed after the patient passed a clamp trial, and a subsequent chest x-ray the next day showed no evidence of recurrence.

On the second day of hospitalization, the patient complained of severe abdominal pain and constipation, although she was passing gas and denied nausea or vomiting. Significant abdominal distention was noted without rebound or guarding. Over the course of the day, she developed nausea, nonbloody and nonbilious emesis, and an increase in fetal heart rate from the 130s to 160s observed during electronic fetal monitoring. Maternal vital signs were notable for ongoing hypertension and worsening tachycardia with a low-grade fever. Laboratory studies demonstrated normal white blood cell counts, hemoglobin, amylase, lipase, hepatic function tests, creatinine, lactate, fibrinogen, and other coagulation markers. Magnetic resonance imaging of the abdomen and pelvis revealed dilated segments of large bowel without obstructing lesions and left-sided renal lesions suggestive of lipid-poor angiomyolipomas (Figure 2). Given the combination of spontaneous pneumothorax, cystic lung lesions, and renal angiomyolipomas, a diagnosis of lymphangioleiomyomatosis (LAM) was made in consultation with radiology and pulmonology. The patient did not have any family history or other symptoms to suggest tuberous sclerosis.

After remaining clinically stable with improved vital signs and reassuring fetal well-being over the subsequent day, the patient experienced worsening abdominal pain and distention on the fourth day of hospitalization with progressive bilious emesis. The fetus, now at 30 weeks and 2 days gestation, was noted concurrently to have numerous late and prolonged decelerations during routine monitoring. Because of clinical concern for concealed placental abruption in the setting of preeclampsia with severe features, the decision was made to proceed with delivery, which was accomplished via cesarean delivery because of fetal malpresentation.

FIGURE 2
MRI of abdomen demonstrating renal lesions



MRI, magnetic resonance imaging.

Wang-Koehler. Lymphangioleiomyomatosis in pregnancy. Am J Obstet Gynecol Glob Rep 2024.

Before proceeding to the operating room, a nasogastric tube was placed, which produced 1 L of bilious output immediately upon connection to low continuous wall suction. The primary cesarean delivery itself was uncomplicated with no evident signs of placental abruption. The bowel was examined and noted to be dilated throughout, although pink and seemingly healthy. Milky ascites, possibly consistent with chyle, were noted at the time of peritoneal entry, but could not be appropriately sampled given the urgency of delivery and subsequent intermixing with blood and amniotic fluid. The male neonate, weighing 1836 grams, was transferred to the neonatal intensive care unit (NICU) for further management of prematurity with Apgar scores of 4 and 8 at 1 and 5 minutes of life, respectively.

On the first postoperative day, the patient's abdominal distension and pain persisted. A CT scan of the abdomen and pelvis with oral contrast demonstrated small bowel dilation concerning for possible small bowel obstruction or ileus. The patient also had acute kidney injury (creatinine level, 1.53 mg/dL), tachycardia (120−140 beats per minute), a fever (to 104°F), and leukopenia (nadir 3.4×10^9/L) concerning for sepsis and was started on empiric broad spectrum antibiotics with vancomycin and cefepime. The patient then developed atrial fibrillation with rapid ventricular response and was started on amiodarone with transfer to the surgical intensive care unit (ICU) for further management. After the arrhythmia was controlled, the patient remained in the ICU for several days with continued severe abdominal pain and distension and copious output from the nasogastric tube. On postoperative day 4, a repeat CT scan noted a small bowel obstruction with free air under the diaphragm concerning for bowel perforation. She was taken urgently to the operating room where a cecal perforation was found. The general surgery division performed an ileocecectomy, and the bowel was left in temporary discontinuity with open fascia and a plan to return to the operating room in several days for re-evaluation. The patient ultimately required a right hemicolectomy with end ileostomy. It was hypothesized that the precipitant of her bowel disease was peritonitis secondary to chylous ascites, which triggered refractory bowel dilation distal to the cecum and ultimately a spontaneous perforation.

The patient's postoperative course was also complicated by a peri-splenic abscess that required drainage, a pulmonary embolism, and a recurrent right pneumothorax that necessitated repeated chest tube replacement. The patient was followed closely by the surgery, pulmonology, interventional radiology, and maternal-fetal medicine divisions throughout the extended hospital course, during which time the patient spent 10 days in the ICU. After a prolonged hospitalization, the patient was stable for discharge to acute rehabilitation on hospital day 37. The neonate did well in the NICU and was discharged home on hospital day 66.

Literature review

A systematic literature review was conducted using OVID, Scopus, Embase, and PubMed databases with the aid of Covidence software. Studies and case reports were identified using the Medical Subject Headings search terms "pregnancy" or "pregnan*" and "lymphangioleiomyomatosis" from the inception of the database through October 2022. The search was limited to English language articles only. Studies were included if they described a diagnosis of pulmonary lymphangioleiomyomatosis and its relationship with clinical or obstetrical outcomes within the context of pregnancy or the immediate postpartum period. A total of 217 studies were imported for screening, and 102 duplicates were removed. A total of 57 full-text studies were then assessed for eligibility of which 28 were excluded (Figure 3). Ultimately, 29 studies were included in this review and the relevant data were abstracted with a particular focus on obstetrical outcomes and medical complications during pregnancy.

Results

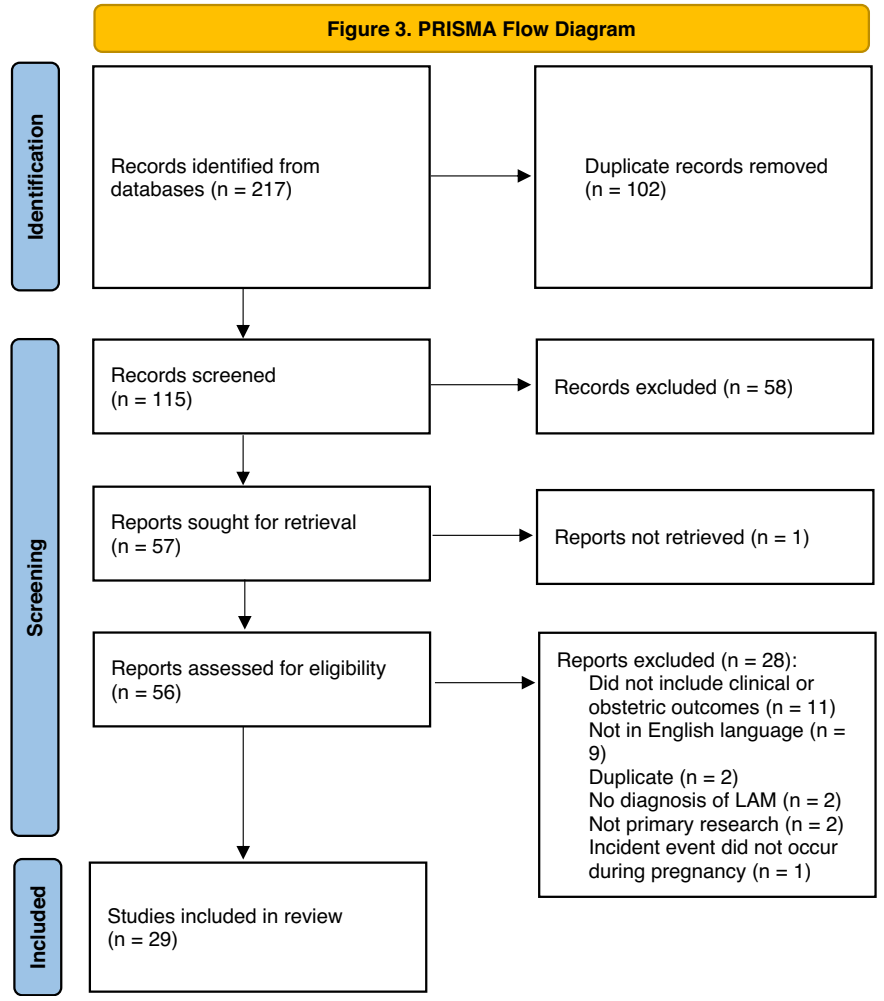
Of the 29 studies reviewed, the majority (24) were case reports that described LAM during pregnancy. Of the remaining studies, 1 was a descriptive chart review, 2 were survey questionnaires, 1 was a combined chart review and survey, and 1 was a national observational cohort study.

Case report summary

Of the case reports, most cases presented with symptoms during pregnancy and were diagnosed with LAM either during or shortly after pregnancy (see Table 1[2−25]). Six women had diagnoses preceding the pregnancy, 2 of whom did not report any symptoms during the pregnancy.[10,11] Two were also diagnosed with tuberous sclerosis. The median age of presentation with symptoms was 29.5 years, and the median gestational age at presentation was 20.5 weeks with case presentations evenly distributed across all trimesters. A total of 12 cases were primiparous and 5 were multiparous, although the parity for 7 cases was not reported. Dyspnea (12), cough (6), chest or shoulder pain (2), hemoptysis (2), flank pain (2), and hypoxia (2) were the most commonly reported presenting signs or symptoms. A total of 11 of 24 cases reported pneumothoraces during pregnancy, 4 of which recurrent episodes. Only 1 case had chylothorax or chylous ascites during pregnancy. Nine cases had renal angiomyolipomas that were present during pregnancy. Six cases reported concomitant obstetrical complications, including preeclampsia, fetal growth restriction, placenta previa, and preterm labor, whereas 7 cases had other medical complications related to LAM (including re-intubation, pulmonary hypertension, acute respiratory distress syndrome, and pulmonary infection). In total, 75% of patients received some invasive intervention, including a chest tube, pleurodesis, thoracostomy or thoracotomy, extracorporeal membrane oxygenation, nephrectomy, or embolization of AMLs.

In terms of delivery, nearly 83% (20/24) of patients delivered by cesarean delivery. Among those whose cesarean delivery indication was reported, 8 were planned or elective cesarean deliveries in anticipation of poor outcomes related

FIGURE 3
PRISMA flow diagram



LAM, lymphangeioleiomyomatosis; *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Wang-Koehler. Lymphangioleiomyomatosis in pregnancy. Am J Obstet Gynecol Glob Rep 2024.

to LAM, 5 were for an obstetrical indication (preeclampsia, FGR, placenta previa, failure to progress in labor), and 4 were unplanned in response to a LAM complication, such as pneumothorax or worsening dyspnea. Of the 2 reported vaginal deliveries, neither developed a pneumothorax during labor. The median gestational age at delivery was 35.5 weeks and half delivered in the preterm period. Fetal outcomes were not reported in many cases, but the majority of those reported were healthy; 1 was a fetal demise at 9 months, 1 was an abortion because of worsening maternal clinical status at 20 weeks' gestation, and 1 was a neonatal death because of prematurity at 25 weeks' gestation.

Study summary

A total of 5 studies were included in the literature review with results mirroring the case reports (Table 2[26–30]). Two survey studies[26,28] demonstrated that more women diagnosed with LAM before or during pregnancy either avoided pregnancy or had an abortion because of concern for LAM complications. Per patient report, these same 2 studies demonstrated higher rates of miscarriages, including those on sirolimus,[26,29] although 1 additional study of patients with tuberous sclerosis did not demonstrate this.[28] Studies demonstrated that those diagnosed with LAM during pregnancy were at higher risk for maternal respiratory or renal complications[26,29] and that the incidence of complications was also higher during pregnancy than at other times.[27,30] Of those who reported delivery outcomes, the majority were cesarean deliveries with an increased incidence of premature births, although it was unclear if these were iatrogenic.

Discussion

LAM primarily affects younger adult women with an average age at onset of around 35 years, and it is known that estrogen plays a key role in driving LAM cell proliferation. Pregnancy itself can exacerbate LAM symptoms as evidenced by this literature review. Patients with LAM diagnosed before and during pregnancy have a greater risk of LAM-associated complications during pregnancy, including a pneumothorax, chylous effusion, exacerbation of dyspnea, and spontaneous bleeding of renal angiomyolipomas. As with the patient in this case report, these complications can contribute to severe maternal morbidity, prolonged hospitalizations, and multiple interventions with long-term consequences on health. Our patient's LAM was completely asymptomatic and unknown before pregnancy but rapidly became clinically significant and contributed to the complications that occurred during pregnancy and the postpartum period. Although her recurrent pneumothoraces were directly related to LAM, the reason behind her bowel perforation remains unclear. Bowel perforation is an extremely rare event during pregnancy of which there are only a few case reports. Mechanisms of injury that have been described include endometriosis, bowel obstruction, peritonitis, stercoral perforation, and inflammatory bowel disease.[31] Although several case reports have demonstrated an association between chylous ascites and intestinal obstruction or perforation, this is the first case report of bowel perforation in the context of LAM and specifically during pregnancy.[32,33]

It is unclear whether LAM diagnosed during pregnancy inherently presents as a more aggressive disease or why pregnancy triggers a LAM flare up in some

TABLE 1
Case reports of LAM and pregnancy

Authors	Maternal age	Parity	Diagnosis preceding pregnancy?	GA at presentation or worsening symptoms	Presenting symptoms during pregnancy	Complications of LAM during pregnancy	Other pregnancy complications	Treatment and/or interventions	Delivery mode	Indication for CD	GA at delivery (wk)	Term or preterm	Neonatal outcome
Agrawal et al,[3] 2020	29	Unknown	No	28	Dyspnea, hypoxia	Pneumothorax, bronchopleural fistula	Preeclampsia, fetal growth restriction	Chest tube and Heimlich flutter valve, postdelivery sirolimus	Cesarean	Unplanned, worsening preeclampsia	Unknown	Unknown	Unknown
Alkemade et al,[2] 2021	36	Primiparous	No	39	Dyspnea, shoulder or chest pain, cough	Pneumothorax	None	None, spontaneous resolution of pneumothorax	Cesarean	Planned, elective	39	Term	Healthy
Brunelli et al,[4] 1996	26	Unknown	No	35	Dyspnea	Chylothorax	None	Bilateral closed tube thoracostomy, TPN, ligation of lymphatic channels	Cesarean	Unplanned, severe dyspnea secondary to chylothorax	35	Preterm	Unknown
Cho et al,[5] 2009	33	Multiparous	No	39	Hypoxia	Renal angiomyolipoma, tuberous sclerosis	Placenta previa	Intubation, ICU transfer because of hypoxia	Cesarean	Placenta previa	39	Term	Healthy
Cleary-Goldman et al,[6] 2004	23	Primiparous	Yes	26	Dyspnea, cough	Renal angiomyolipoma	Pulmonary infection	Bilateral renal stents, levofloxacin, supplemental oxygen, and albuterol	Cesarean	Planned, elective, concern for renal rupture with hemorrhage	34	Preterm	Healthy
Crawford et al,[7] 2015	37	Primiparous	No	21	Dyspnea, cough, fever	None	ARDS, influenza, preeclampsia, and HELLP syndrome	Bronchoscopy, antibiotics and oseltamivir, V-V ECMO, steroid therapy, recombinant activated factor VII; sirolimus	Cesarean	Unplanned, worsening preeclampsia	24	Preterm	Healthy
Creagh-Brown et al,[8] 2006	37	Multiparous	No	14	Dyspnea	Recurrent pneumothorax	None	Pneumothorax aspiration, VATs and pleurodesis	Cesarean	Unknown	Term	Term	Healthy
Faehling et al,[9] 2011	29	Primiparous	Yes	21	Dyspnea, cough	Pneumothorax	None	Chest tube, sirolimus, chest tube, pleurectomy and resection	Cesarean	Unplanned, secondary to pneumothorax	32	Preterm	Healthy
Faehling et al,[10] 2015	34	Multiparous	Yes	N/A	N/A stable lung function on sirolimus	None	None	Sirolimus	Cesarean	Unknown	32	Preterm	Healthy
Fujimoto et al,[11] 2005	30	Primiparous	Yes	N/A	N/A	None	None	N/A	Cesarean	Planned, concern for spontaneous pneumothorax	38	Term	Healthy
Gargari et al,[12] 2009	35	Multiparous	No	8	Dyspnea	None	None	None	Cesarean	Planned, elective	37	Term	Healthy
Iruloh et al,[13] 2013	23	Primiparous	No	31	Dizziness, blurry vision, dyspnea, fatigue, itching	Renal angiomyolipoma	None	Coil and particle embolization of angiomyolipoma after cesarean delivery	Cesarean	Planned, elective	38	Term	Unknown

Wang-Koehler. Lymphangioleiomyomatosis in pregnancy. Am J Obstet Gynecol Glob Rep 2024.

(continued)

TABLE 1
Case reports of LAM and pregnancy *(continued)*

Authors	Maternal age	Parity	Diagnosis preceding pregnancy?	GA at presentation or worsening symptoms	Presenting symptoms during pregnancy	Complications of LAM during pregnancy	Other pregnancy complications	Treatment and/or interventions	Delivery mode	Indication for CD	GA at delivery (wk)	Term or preterm	Neonatal outcome
John et al,[14] 2022	29	Unknown	No	37	Constipation, abdominal pain	Renal angiomyolipoma	None	Left nephrectomy	Cesarean	Unplanned, likely in setting of renal mass	37	Term	Unknown
Johnston et al,[15] 2011	18	Primiparous	No	20	Dyspnea, fatigue	None	Fetal growth restriction	Bilateral chest tubes, thoracoscopy with lung stapling, eventual lung transplant	Cesarean	Fetal growth restriction	29	Preterm	Unknown
McCartney et al,[16] 2009	30	Multiparous	No	19	Dyspnea	Recurrent pneumothorax	None	Aspiration of pneumothorax, chest drain placement, VATs, left-sided pleurodesis	Cesarean	Unplanned, history of cesarean delivery, worsening clinical status	34	Preterm	Healthy
McLoughlin et al,[17] 2003	29	Primiparous	Yes	4	Flank pain	Renal angiomyolipoma	None	Enucleation of angiomyolipoma without nephrectomy after delivery	Vacuum-assisted vaginal delivery	Planned, elective	39	Term	Unknown
Mitra et al,[18] 2004	30	Unknown	No	8	Dyspnea, cough	None	Right ventricular failure with pulmonary hypertension	Pulmonary HTN treated with oxygen, antibiotics and diuretics; medroxyprogesterone	Vaginal	N/A	36	Preterm	Fetal demise at 9 mo
Pais et al,[19] 2017	26	Unknown	No	Unknown	Cough, hemoptysis	Renal angiomyolipoma	None	Hypoxia requiring supplemental oxygen	Cesarean	Planned, concern for neonatal or maternal adverse outcomes	30	Preterm	Unknown
Peces et al,[20] 2011	25	Primiparous	No	12	Flank pain	Renal angiomyolipoma, tuberous sclerosis	None	Embolization of renal AMLs and radical left nephrectomy, sirolimus	Cesarean	Planned, elective	38	Term	Healthy
Toyoda et al,[21] 2006	26	Primiparous	No	27	Hemoptysis, chest pain	Recurrent pneumothorax, renal angiomyolipoma	Idiopathic thrombocytopenia	ITP requiring IVIG. Recurrent pneumothorax leading to chest tube and VATs postpartum; home oxygen, leuprolide	Cesarean	Unknown	35	Preterm	Healthy
Weinans and van Loon,[22] 1999	30	Primiparous	No	10	Abdominal pain, fatigue, general malaise, weight loss	Renal angiomyolipoma	None	Exploratory laparotomy of retroperitoneal mass, oxygen therapy, medroxyprogesterone	Cesarean	Failure to progress in first stage of labor	39	Term	Healthy
Wilson et al,[23] 2001	24	Unknown	No	6	Unknown, spontaneous pneumothorax	Recurrent pneumothorax	Preterm labor	Abrasion pleurodesis of pneumothorax, kaolin insufflation; vaginal progesterone, medroxyprogesterone	Unknown	N/A	25	Preterm	Neonatal death

Wang-Koehler. Lymphangioleiomyomatosis in pregnancy. Am J Obstet Gynecol Glob Rep 2024.

(continued)

TABLE 1
Case reports of LAM and pregnancy *(continued)*

Authors	Maternal age	Parity	Diagnosis preceding pregnancy?	GA at presentation or worsening symptoms	Presenting symptoms during pregnancy	Complications of LAM during pregnancy	Other pregnancy complications	Treatment and/or interventions	Delivery mode	Indication for CD	GA at delivery (wk)	Term or preterm	Neonatal outcome
Yamashita et al,[24] 2011	30	Primiparous	Yes	36	Unknown, pneumothorax	Pneumothorax	None	Chest tube, delivery; GnRH analogue after delivery	Cesarean	Planned, concern for progression of pneumothorax in labor	37	Term	Healthy
Yockey et al,[25] 1986	33	Unknown	No	18	Dyspnea	Pneumothorax	Preterm labor; obstructive hydronephrosis, acute respiratory failure requiring intubation, mesangial proliferative glomerulonephritis	Left thoracotomy during pregnancy; chest tube, Tamoxifen and Provera. Ultimately required pleurectomy and pleurodesis	TAH/BSO	Obstructed labor secondary to massive fibroid—inability to evacuate uterus and thought that placental or ovarian estrogen production was stimulating disease	20	Preterm	Abortion

AML, angiomyolipoma; *ARDS*, acute respiratory distress syndrome; *BSO*, bilateral salpingo-oophorectomy; *CD*, cesarean delivery; *GA*, gestational age; *GnRH*, gonadotropin-releasing hormone; *HELLP*, hemolysis, elevated liver enzymes, low platelet count; *HTN*, hypertension; *ICU*, intensive care unit; *ITP*, immune thrombocytopenic purpura; *IVIG*, intravenous immune globulin; *LAM*, lymphangioleiomyomatosis; *N/A*, not applicable; *TAH*, total abdominal hysterectomy; *TPN*, total parenteral nutrition; *VATs*, video-assisted thoracic surgery; *V-V ECMO*, venovenous extracorporeal membrane oxygenation.

Wang-Koehler. Lymphangioleiomyomatosis in pregnancy. Am J Obstet Gynecol Glob Rep 2024.

but not others. AMLs may also be at greater risk for rupture during pregnancy and should be serially monitored with imaging. In nonpregnant patients, the current guidelines recommend embolization if the AML size exceeds 4 to 8 cm.[34] However, the optimal threshold for intervention during pregnancy remains uncertain.

This review also demonstrates the impact of a LAM diagnosis on obstetrical outcomes, with specific emphasis on the high cesarean delivery and preterm birth rate. Although many of these cesarean deliveries were in response to an obstetrical indication or worsening maternal clinical status, a sizable proportion were also elective given the risk of LAM-associated complications. Overall, the fetal outcomes were favorable despite an increased incidence of prematurity. Still, this highlights the combined medical and obstetrical morbidity rate associated with LAM during pregnancy.

The diagnosis of LAM has several implications for patient counseling and treatment related to pregnancy. Female patients with LAM are often advised to avoid pregnancy given the risks for worsening symptoms, pneumothorax, and preterm birth. Successful pregnancy management requires multidisciplinary collaboration among specialists in maternal-fetal medicine, pulmonology, anesthesia, and possibly nephrology, neurology, and cardiology, depending on the associated symptoms. Pregnant patients with LAM are typically recommended to obtain pulmonary function tests every 3 months. In addition, if there are signs of hereditary tuberous sclerosis, such as personal or family history of characteristic skin lesions, seizures, or intellectual disability, additional counseling about genetic testing for the patient and the fetus should be provided. There is no consensus about the optimal mode of delivery in patients with LAM. However, given an increased risk for pneumothorax with increased intrathoracic pressure during labor, epidural analgesia with a low threshold to perform an operative vaginal delivery may be advisable, even if the patient has already undergone pleurodesis for a

TABLE 2
Summary of studies on LAM and pregnancy

Authors	Type of study	Population	Outcomes	Main results
Cohen et al,[26] 2009	Survey questionnaire	328 women with LAM	Pregnancy outcomes, pulmonary function, subjective and psychological functioning, quality of life, dyspnea and fatigue	Pregnancy outcomes 37.3% of women had never been pregnant; 55% of women without children avoided pregnancy because of concern about impact of pregnancy on LAM; 3% worried about TSC and passing it onto child; 8.2% were unable to have children despite trying. 178/346 (51%) of women were diagnosed with LAM more than a year after completing their pregnancies, 15 women (4.5%) were diagnosed with LAM during a pregnancy, and 12 (3.6%) women had 15 pregnancies after they were diagnosed with LAM. Patients diagnosed with LAM during pregnancy had significantly more premature births and miscarriages (53%) than those diagnosed before pregnancy (20%) or after (15%). More women with an existing or emerging diagnosis of LAM during pregnancy had their pregnancies terminated (17%) than women diagnosed after pregnancy (7%). LAM complications 66.7% of those diagnosed during pregnancy experienced a pneumothorax vs 26% of those diagnosed before or 5.2% of those diagnosed after pregnancy. This was similar for breathlessness (66.7% vs 6.7% vs 7.2%, respectively). There was no difference in subjective and psychological functioning, quality of life, fatigue, or dyspnea among women diagnosed before, during, or after pregnancy.
Johnson and Tattersfield,[27] 2000	Chart review	50 women with LAM without TSC within a 5-y period	Disease duration, incidence of complications (pneumothoraces, chylous effusions, related thoracic surgical procedures), type of treatment, lung function	28/50 (56%) patients had been pregnant; 7 (25%) were diagnosed with LAM before or during pregnancy or the postpartum period. Pregnancy outcomes 4/7 (57%) pregnancies were delivered by cesarean delivery, 1 of which was preterm. LAM complications Of these, 5 (71%) had complications; 2 developed chylous pleural effusions and 3 had 1 or more pneumothoraces. Three required lung surgery during pregnancy. Incidence of complications was 11 times higher during pregnancy than at other times (CI, 5.3−25.0; $P<.001$).
Mitchell et al,[28] 2003	Survey questionnaire	145 women with tuberous sclerosis complex	Renal involvement (cysts, AML on imaging) and complications (hypertension, hemorrhage, pain, rupture, renal failure, treatments). Pulmonary involvement (cysts or LAM on imaging) and complications (pneumothorax). Pregnancy outcomes	Pregnancy outcomes 81% of pregnancies were live births, 13.5% were miscarriages, 3% were abortions, 0.4% were ectopic pregnancy, 1.5% were stillbirths (1 secondary to uterine rupture in a woman with renal involvement, 1 secondary to AML rupture and severe blood loss, 1 related to malnutrition secondary to celiac disease, 1 with unknown causes). There were no maternal deaths. 89% of those who experienced pregnancy-related AML hemorrhages delivered live born infants. Renal involvement 67 women with renal involvement had at least 1 pregnancy. 57% had renal complications, majority after pregnancy. Of renal complications during pregnancy, 8 had hemorrhage 2/2 RAML. There was no significant difference in the rate of renal complications (57% vs 67%; $P=.62$) for pregnant and never-pregnant groups. Pulmonary involvement 22% of women with pregnancies had pulmonary involvement. 40% women experienced a pneumothorax, the majority after pregnancy. There was no significant difference in pneumothorax (40% vs 38%; $P=1.00$) for the pregnant and never-pregnant groups.

Wang-Koehler. Lymphangioleiomyomatosis in pregnancy. Am J Obstet Gynecol Glob Rep 2024.

(continued)

TABLE 2
Summary of studies on LAM and pregnancy *(continued)*

Authors	Type of study	Population	Outcomes	Main results
Shen et al,[29] 2021	Chart review and survey questionnaires	30 women with total of 34 pregnancies after LAM diagnosis	Complications of LAM (pneumothorax, chlyothorax, AML bleeding), sirolimus usage, pregnancy outcomes	Pregnancy outcomes 29% were live births, 18% were miscarriages, 53% were abortions (reasons included pneumothorax, sirolimus history, worries about LAM complications). LAM complications Complications occurred in 29.4% of patients. 20% reported worsening dyspnea, 9% pneumothorax, 6% bleeding AMLs, 0% chylothorax. Sirolimus treatment Sirolimus treatment was common (50%). 6/34 patients had livebirths after taking sirolimus; 3 discontinued prior to pregnancy and 3 were taking sirolimus at time of discovery of pregnancy, with subsequent discontinuation.
Taveira-DaSilva et al,[30] 2020	National observational cohort study	16 women with LAM and pre- and postpregnancy data	Lung function and CT scans before and after pregnancy	Pregnancy outcomes 25% were vaginal and 75% were cesarean deliveries. 12.5% complicated by preeclampsia. All gave birth to healthy babies. LAM complications 31% developed pneumothorax during pregnancy. Pregnancy was associated with a decrease in lung function, and cyst severity scores on imaging increased for all cases after pregnancy. This was two-fold greater than non-pregnant women with LAM.

AML, angiomyolipoma; *CI*, confidence interval; *CT*, computed tomography; *LAM*, lymphangioleiomyomatosis; *RAML*, renal angiomyolipoma; *TSC*, tuberous sclerosis.

Wang-Koehler. Lymphangioleiomyomatosis in pregnancy. Am J Obstet Gynecol Glob Rep 2024.

previous pneumothorax because of the risk for recurrence.[35] An elective cesarean delivery is also an option, and, from this review, it seems that many opt for this route, possibly because of the extent of the risk that patients or physicians are willing to undertake with labor.

In terms of long-term treatment, sirolimus, an mTOR inhibitor that is typically used to prevent kidney transplant rejection, has been found to be a beneficial therapy to stabilize lung function and improve quality of life in LAM patients. However, safety data on sirolimus in pregnancy and lactation are limited. Current recommendations from the drug manufacturer are to discontinue sirolimus 12 weeks before pregnancy; however, 1 study found no congenital anomalies after brief exposure during pregnancy,[29] and there is 1 known case report of sirolimus that was continued throughout pregnancy without complication.[10] Given its immunosuppressant effects and impact on wound healing, sirolimus is usually withheld in the setting of severe infection and before surgeries, such as cesarean delivery. Currently, outside of pregnancy, it is only recommended for patients with LAM who have more advanced or rapidly declining lung disease or those with active chylous effusions. Its potential for benefit in the setting of prevention and/or treatment of LAM flare ups in pregnancy is unknown.

Patients should also be counseled to avoid estrogen-containing contraceptives. In the past, medroxyprogesterone was administered to reduce circulating estrogen levels; however, there are no studies supporting that progesterone improves pulmonary function or the natural history of LAM disease progression.[36] Postmenopausal women should avoid hormone replacement therapy.

In summary, our patient initially presented in the third trimester of pregnancy with acute chest pain, which was found to be secondary to a pneumothorax, and the ultimate cause was determined to be LAM. A spontaneous pneumothorax itself in pregnant women is rare and should be investigated with a broad differential diagnosis,

including LAM.[37] This patient's overall clinical course was impacted by multiple complicating factors, including recurrent pneumothorax, severe preeclampsia, atrial fibrillation, pulmonary embolism, and bowel dilation and perforation. Although all these complications may not be directly related to LAM, it is clear that the acute diagnosis of LAM played a significant causative role in this previously healthy patient's severe maternal morbidity and preterm birth. From the literature review it is clear that this case outcome is not uncommon; many women diagnosed with LAM during pregnancy will experience some sort of prolonged hospitalization and morbidity. Of course, this review is limited by case report selection bias, which may skew toward more morbid clinical courses. Still, these outcomes align with registry and survey studies on pregnancy and LAM. Thus, for patients with a clinical suspicion of a new diagnosis of LAM in pregnancy, prompt recognition, diagnosis, and referral to appropriate multidisciplinary subspecialists is critical to mitigate complications and optimize outcomes, both during and after pregnancy. ■

CRediT authorship contribution statement

Eileen Wang-Koehler: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Adina R. Kern-Goldberger:** Conceptualization, Supervision, Writing – review & editing. **Sindhu K. Srinivas:** Conceptualization, Supervision, Writing – review & editing.

REFERENCES

1. Hohman DW, Noghrehkar D, Ratnayake S. Lymphangioleiomyomatosis: a review. Eur J Intern Med 2008;19:319–24.

2. Alkemade L, Berghuis MAT, Koopman B, van Pampus MG. Initial presentation of lymphangioleiomyomatosis in third trimester of pregnancy. BMJ Case Rep 2021;14:e237824.

3. Agrawal A, Karle E, Patel TP, et al. A pregnant woman presenting with progressively worsening dyspnea and pneumothorax. Chest 2020;157:e193–6.

4. Brunelli A, Catalini G, Fianchini A. Pregnancy exacerbating unsuspected mediastinal lymphangioleiomyomatosis and chylothorax. Int J Gynaecol Obstet 1996;52:289–90.

5. Cho SY, Kim KH, Jeon WJ. Caesarean delivery under general anaesthesia for a woman with undiagnosed tuberous sclerosis complex and lymphangioleiomyomatosis. Anaesth Intensive Care 2009;37:142–3.

6. Cleary-Goldman J, Sanghvi AV, Nakhuda GS, Robinson JN. Conservative management of pulmonary lymphangioleiomyomatosis and tuberous sclerosis complicated by renal angiomyolipomas in pregnancy. J Matern Fetal Neonatal Med 2004;15:132–4.

7. Crawford TC, Grimm JC, Magruder JT, et al. A curious case of acute respiratory distress syndrome. J Surg Case Rep 2015;2015:rjv140.

8. Creagh-Brown B, Cooke N, Corbishley C. Conservative management of an unusual cause of breathlessness during pregnancy. Respir Med Extra 2006;2:116–9.

9. Faehling M, Frohnmayer S, Leschke M, Trinajstic-Schulz B, Weber J, Liewald F. Successful pregnancy complicated by persistent pneumothorax in a patient with lymphangioleiomyomatosis (LAM) on sirolimus. Sarcoidosis Vasc Diffuse Lung Dis 2011;28:153–5.

10. Faehling M, Wienhausen-Wilke V, Fallscheer S, Trinajstic-Schulz B, Weber J, Leschke M. Long-term stable lung function and second uncomplicated pregnancy on sirolimus in lymphangioleiomyomatosis (LAM). Sarcoidosis Vasc Diffuse Lung Dis 2015;32:259–64.

11. Fujimoto M, Ohara N, Sasaki H, et al. Pregnancy complicated with pulmonary lymphangioleiomyomatosis: case report. Clin Exp Obstet Gynecol 2005;32:199–200.

12. Saleh Gargari S, Hantoushzadae S, Mohamadi F, Jafar-Abadi M. Pregnancy complicated by lymphangioleiomyomatosis. Arch Iran Med 2009;12:182–5.

13. Iruloh C, Keriakos R, Smith DJ, Cleveland T. Renal angiomyolipoma and lymphangioleiomyomatosis in pregnancy. J Obstet Gynaecol 2013;33:542–6.

14. John J, Aldera AP, Louw D, Lazarus J, Kesner K. Pulmonary lymphangioleiomyomatosis with an associated giant renal angiomyolipoma. Ther Adv Urol 2022;14:17562872211069700.

15. Johnston CR, O'Donnell ME, Sayed Ahmed WA, Hunter A, Graham AN. Bilateral pneumothorax in pregnancy unmasking lymphangioleiomyomatosis. Ir J Med Sci 2011;180:933–4.

16. McCartney R, Facey N, Chalmers G, et al. Multiple pneumothoraces during second and third trimesters as first presentation of lymphangioleiomyomatosis. Obstet Med 2009;2:84–6.

17. McLoughlin L, Thomas G, Hasan K. Pregnancy and lymphangioleiomyomatosis: anaesthetic management. Int J Obstet Anesth 2003;12:40–4.

18. Mitra S, Ghosal AG, Bhattacharya P. Pregnancy unmasking lymphangioleiomyomatosis. J Assoc Physicians India 2004;52:828–30.

19. Pais F, Fayed M, Evans T. Lymphangioleiomyomatosis: an explosive presentation of a rare disease. Oxf Med Case Reports 2017;2017:omx023.

20. Peces R, Cuesta-López E, Peces C, Selgas R. Giant bilateral renal angiomyolipomas and lymphangioleiomyomatosis presenting after two successive pregnancies successfully treated with surgery and rapamycin. ScientificWorldJournal 2011;11:2115–23.

21. Toyoda K, Matsumoto K, Inoue H, et al. A pregnant woman with complications of lymphangioleiomyomatosis and idiopathic thrombocytopenic purpura. Intern Med 2006;45:1097–100.

22. Weinans MJN, van Loon AJ. A diagnosis of lymphangioleiomyomatosis in a pregnant woman presenting with a retroperitoneal mass. Br J Obstet Gynaecol 1999;106:747–8.

23. Wilson AM, Slack HL, Soosay SA, et al. Lymphangioleiomyomatosis a series of three case reports illustrating the link with high oestrogen states. Scott Med J 2001;46:150–2.

24. Yamashita S, Nakamura K, Shinozaki H, Minegishi T. Lymphangioleiomyomatosis suspected to be a gynecologic disease. J Obstet Gynaecol Res 2011;37:267–9.

25. Yockey CC, Riepe RE, Ryan K. Pulmonary lymphangioleiomyomatosis complicated by pregnancy. Kans Med 1986;87:277–93.

26. Cohen MM, Freyer AM, Johnson SR. Pregnancy experiences among women with lymphangioleiomyomatosis. Respir Med 2009;103:766–72.

27. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. Thorax 2000;55:1052–7.

28. Mitchell AL, Parisi MA, Sybert VP. Effects of pregnancy on the renal and pulmonary manifestations in women with tuberous sclerosis complex. Genet Med 2003;5:154–60.

29. Shen L, Xu W, Gao J, et al. Pregnancy after the diagnosis of lymphangioleiomyomatosis (LAM). Orphanet J Rare Dis 2021;16:133.

30. Taveira-DaSilva AM, Johnson SR, Julien-Williams P, Johnson J, Stylianou M, Moss J. Pregnancy in lymphangioleiomyomatosis: clinical and lung function outcomes in two national cohorts. Thorax 2020;75:904–7.

31. Chuang MT, Chen TS. Bowel obstruction and perforation during pregnancy: case report and literature review. Taiwan J Obstet Gynecol 2021;60:927–30.

32. Akama Y, Shimizu T, Fujita I, et al. Chylous ascites associated with intestinal obstruction from volvulus due to Petersen's hernia: report of a case. Surg Case Rep 2016;2:77.

33. Lim HW, Sultan KS. Sclerosing mesenteritis causing chylous ascites and small bowel perforation. Am J Case Rep 2017;18:696–9.

34. Murray TE, Doyle F, Lee M. Transarterial embolization of angiomyolipoma: a systematic review. J Urol 2015;194:635–9.
35. Hallifax RJ, Yousuf A, Jones HE, Corcoran JP, Psallidas I, Rahman NM. Effectiveness of chemical pleurodesis in spontaneous pneumothorax recurrence prevention: a systematic review. Thorax 2017;72:1121–31.
36. Khaddour K, Shayuk M, Ludhwani D, Gowda S, Ward WL. Pregnancy unmasking symptoms of undiagnosed lymphangioleiomyomatosis: case report and review of literature. Respir Med Case Rep 2018;26:63–7.
37. Lateef N, Dawood M, Sharma K, Tauseef A, Munir MA, Godbout E. Recurrent spontaneous pneumothorax in pregnancy – a case report and review of literature. J Community Hosp Intern Med Perspect 2018;8:115–8.