INTRODUCTION

Influenza infections are caused by the ribonucleic acid (RNA) viruses influenza-A, B, and C. These infections typically occur seasonally and frequently lead to respiratory infection and fever.\(^1\)\(^2\) Typically, influenza is a common and self-limiting disease; however, in specific populations, such as pregnant women, a higher prevalence of complications has been observed.\(^3\) Pregnant women with influenza-A are more susceptible to developing acute respiratory distress syndrome (ARDS). Extracorporeal membrane oxygenation (ECMO) can be used as salvage therapy, with lung transplantation as a therapeutic option. However, successful bilateral lung transplantation during pregnancy has never been reported before.

We herein report the case of a 34-year-old primipara, who was diagnosed with ARDS caused by influenza-A-induced pneumonia at early gestation. After considering all possible therapeutic options and being fully dependent on VV-ECMO support, she underwent bilateral lung transplantation. The transplantation with intraoperative central VA-ECMO support was successfully performed with good recovery after an initial primary graft dysfunction. The pregnancy was prolonged until 29\(^1\)\(^5\) gestational weeks. The newborn exhibited growth retardation and was initially stabilized, but later died due to severe, hypoxic respiratory failure and pulmonary hypertension. In conclusion, lung transplantation is a possible salvage therapy for patients with severe lung failure following ARDS during pregnancy. However, it places the mother and unborn child at risk. A multi-professional approach is warranted to diagnose and treat complications at an early stage.
recipients are generally discouraged from becoming pregnant due to an increased risk of transplant rejection, infections resulting from ongoing immunosuppression, pulmonary hypertension, pre-eclampsia, gestational diabetes, and preterm birth, in addition to neonatal complications and maternal and neonatal death. Additionally, to our knowledge, no case has ever been published describing a successful lung transplantation during pregnancy. For this publication, the patient provided full informed consent.

2 | CASE REPORT

In March 2019, a 34-year-old primipara (blood type A+, BMI 24.8 kg/m²) woman was transferred to our tertiary center at 16 + 5 gestational weeks because of ARDS caused by influenza-A-induced pneumonia. She had been intubated 3 weeks prior, and veno-venous extracorporeal membrane oxygenation (VV-ECMO) support was initiated 7 days after intubation. Upon admission, the patient was fully dependent on VV-ECMO support (3.6 L blood flow, 1.0 FiO₂, and 4 L gas flow) and required ventilation with high ventilatory effort (40 mmHg peak inspiratory pressure, 10 mmHg positive end-expiratory pressure). Given the length of ECMO support, the severity of pulmonary radiological changes, and the absence of clinical improvement, her lung damage was considered irreversible (Figure 1). A fetal sonogram at admission showed a normally developed fetus measuring in the 7th percentile, indicating growth retardation. A consensus was reached that the patient should be listed for a bilateral lung transplant, despite being pregnant. Following the presumed will of the sedated patient, consent for transplantation was obtained from her husband and her parents, under the assumption that she wants medically indicated treatment to safe her own life and the life of her baby.

2.1 | Lung transplantation

Two days after being listed for transplantation, at 17 + 0 gestational weeks, a suitable lung donor offer was accepted. The donor was a 67-year-old male (blood type 0+, BMI, 32.6 kg/m²) with a PaO₂/FiO₂ ratio (P/F ratio) of 479 mmHg. Bilateral lung transplantation with intraoperative central VA-ECMO support was performed. The patient exhibited a poor oxygenation index at the end of implantation, suggesting an incipient ischemia-reperfusion injury, and peripheral ECMO support was prolonged into the postoperative period based on our institutional practice. On postoperative day (POD) 3, VA-ECMO could be removed and the graft function was graded as primary graft dysfunction (PGD) 0 at T72, according to the definition of the International Society for Heart and Lung Transplantation (Figure 2). The patient received our institution's standard immunosuppression protocol based on alemtuzumab induction therapy, followed by monotherapy with tacrolimus and steroids. All agents used were considered safe for both the mother and her fetus.

2.2 | Pregnancy and delivery

Between PODs 1 and 18, regular sonograms showed a vital pregnancy with a normal amniotic fluid volume, and the fetus was in the 8th percentile for growth. On POD 19, at 19 + 5 gestational weeks, the amniotic fluid volume had decreased. On POD 20, a vaginal examination ruled out premature preterm rupture of the membranes (pPROM) since no signs of vaginal fluid loss was observed, along with a negative amniotic fluid detection test (AmniSure® rapid immunoassay). An organ scan on POD 24 revealed that the fetus had an estimated weight of 235 g, which was below the 3rd percentile, oligohydramnios, and an intermittent zero flow on the Doppler scan of the umbilical artery. A fetal MRI showed a 50% reduction in fetal lung volume according to the age standard, oligohydramnios, low-grade asymmetry of the lateral ventricles, and intra-amniotic bleeding. The posttransplant recovery of the mother was uneventful, and she was transferred to a pulmonary rehabilitation clinic on POD 44. Due to the reduced likelihood of survival of the fetus with an estimated weight of 315 g at 23 + 1 weeks, the parents requested a "black box approach", meaning no active treatment until 25 + 0 gestational weeks. Afterwards, weekly sonograms were performed while the patient was at the rehabilitation clinic, and all showed a vital fetus with slow weight gain, measuring below the 3rd percentile. The amniotic fluid volume increased constantly and returned to normal on POD 66. Doppler sonography showed positive flow within the normal limits, with increasing pulsatile indices.

FIGURE 1  CT scan of the maternal lungs at the time of listing for transplantation
During a weekly check-up on POD 88, at 29+3 gestational weeks, a zero flow with intermittent reverse flow was identified on a Doppler scan of the umbilical artery. The patient was admitted to the high-risk obstetric ward, and fetal lung maturation with corticosteroids and tocolysis with an oxytocin-receptor antagonist were initiated. On POD 90, an intermittent flow of zero was detected on a Doppler scan of the fetal ductus venosus. Despite the recent maternal lung transplantation and severe intrauterine growth restriction, our multi-professional team suggested to perform a cesarean section (c-section). Magnesium sulfate was initiated for fetal neuroprotection at 29+5 gestational weeks, and a male newborn weighing 800 g (<3rd percentile) was delivered.

Following delivery, her pulmonary function was satisfactory, and no further complications occurred. The newborn had Apgar scores at 1, 5, and 10 min of 8, 9, and 9. The newborn was intubated and mechanically ventilated at an FiO₂ >0.5 3 days after birth. Hydrocortisone therapy was initiated because of decreasing blood pressure. Echocardiography revealed pulmonary hypertension, which was treated with inhaled nitric oxide, iloprost, and sildenafil. The concomitant and deteriorating arterial hypotension was treated with noradrenaline, adrenaline, and vasopressin for 2 days. Due to severe thrombocytopenia, the newborn received thrombocyte concentrates. The newborn was intermittently stabilized, but suffered from frequent, severe hypoxic events and pulmonary hypertensive episodes. Despite the intensive-care approach, the newborn died on postpartum day 5 (POD 95) due to severe hypoxic respiratory failure and severe pulmonary hypertension. Pathology examination confirmed persistent pulmonary hypertension as the cause of death (Figure 3).

2.4 | Pulmonary follow-up

De novo donor-specific anti-human leukocyte antigen (HLA) antibodies (dnDSAs) against HLA-class I antibodies were diagnosed in the early postoperative period. However, the patient did not exhibit any pulmonary symptoms compatible with an antibody-mediated rejection. The dnDSAs resolved after 6 months without any specific treatment. So far, neither high-grade acute cellular rejection nor antibody-mediated rejection were diagnosed. Despite initial improvements in lung function, the patient experienced a slow chronic decrease in forced expiratory volume in the first second to 35%–40% in the absence of other possible etiologies. After a trial with
azithromycin, extracorporeal photopheresis was initiated, which resulted in stabilization of lung function. The patient remains in good clinical condition nearly two years after transplantation.

3 | DISCUSSION

To the best of our knowledge, this is the first case worldwide of a successful bilateral lung transplantation during pregnancy. Influenza-A infection ultimately led to a devastating pulmonary condition that required transplantation. It is well-known that the increased risk for pregnant women to develop influenza-related ARDS is associated with high mortality rates for mothers and fetuses. ECMO can be used as salvage therapy in patients with severe ARDS. Of note, influenza virus infections are the most frequent indications for ECMO therapy during pregnancy. With ECMO, maternal survival ranges from 74.6% to 77.8%, and approximately 66% of fetuses survive. ECMO is therefore considered safe and effective during pregnancy, but should only be maintained until pulmonary recovery, or in the absence of recovery, until lung transplantation. The benefits of ECMO therapy over conventional ventilation remain controversial, suggesting the need for further research comparing therapeutic interventions.

In our patient, different therapeutic options were discussed, including termination of pregnancy, continuation of pregnancy and ECMO-bridge to recovery, and lung transplantation. Termination of pregnancy would have required a c-section under ECMO therapy. Since abdominal surgery procedures under ECMO in critically ill patients are associated with a higher risk of hemorrhage, this approach was not recommended. Continuation of pregnancy under ECMO support was excluded due to the severity of radiological pulmonary changes and the duration of ECMO therapy without improvement. Long-term ECMO support (≥2 weeks) in patients with severe acute respiratory failure is associated with significantly lower rates of complete pulmonary recovery. Therefore, lung transplantation was determined as the only logical therapeutic option. This case demonstrates that significantly improving maternal pulmonary condition with lung transplantation had minimal effects on fetal vitality, though the risk of preterm birth and its associated complications remain an issue.

The pregnancy-related complications that our patient experienced are consistent with those reported in previous studies, including preterm birth, low birth weight, neonatal ARDS, and neonatal death. The observed oligohydramnios was likely caused by maternal diuretic therapy, which induced fetal pulmonary hypoplasia with subsequent pulmonary and arterial hypertension. The unfortunate death of the newborn could be attributed to several events. Oligohydramnios during fetal lung development is associated with lung hypoplasia and consecutive pulmonary hypertension and high neonatal mortality. In particular, the canalicular phase (16–26 gestational weeks) is crucial for the lung function of the neonate, as the capillaries grow and cellular organelles that synthesize lung surfactants are developing. During this phase, mechanical forces influence lung growth maintaining expansion. Oligohydramnios reduces the intrathoracic cavity size and disrupts fetal lung growth, resulting in pulmonary hypoplasia and impaired pulmonary vascular development. These pulmonary vascular changes are more distinctive than parenchymal changes in infants with severe hypoxic failure. In our case, oligohydramnios was identified at 19 gestational weeks and persisted until 26 weeks. It is likely that the acquired lung hypoplasia of the newborn during this time frame led to a failure of the normal circulatory transition at birth and elevated the pulmonary vascular resistance and right-to-left extrapulmonary shunting of deoxygenated blood, resulting in fatal hypoxemia. In future cases, the amount of amniotic fluid should regularly be monitored during ongoing maternal diuretic treatment. The critical phase of fetal lung development should be considered when planning the diuretic regimen for the mother. From an ethical perspective, maternal versus fetal well-being must prioritize maternal over fetal life in critical conditions, especially when complications occur during early pregnancy, when maternal mortality would lead to fetal mortality. In our case, transplantation was crucial for maternal survival, and to allow the pregnancy to continue until the fetus was viable.

In conclusion, our case demonstrates that lung transplantation is a possible salvage therapy for patients with severe lung failure following ARDS during pregnancy. However, transplantation should only be considered if other therapeutic approaches have failed because it places the mother and unborn child at risk. A timely and multi-professional approach is warranted to diagnose and treat complications at an early stage to improve maternal and neonatal outcomes.

ACKNOWLEDGMENTS

The patient has given written informed consent for the publication of this report. The authors want to thank Dr. Maria Kletečka-Pulker for her support.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

AUTHOR CONTRIBUTIONS

This paper was written by PF, KH, AB, KKS, HK, and AF. PF, KH, and AF were responsible for the overall content as guarantors, conceived the idea for this article, and performed the literature research. KH and AB were responsible for writing the thoracic surgery section. KKS composed the neonatology section. HK provided input for obstetrical treatment and outcomes. AS provided information on the pathological reports of the newborn.

ETHICAL STATEMENT

The local ethics committee issued a waiver of approval. Written informed consent was obtained from the patient for publication of this report and any accompanying images. The datasets used and/or analyzed for this report are available from the corresponding author upon reasonable request.
DATA AVAILABILITY STATEMENT

The patient data are available on request to the corresponding author.

ORCID

Philipp Foessleitner https://orcid.org/0000-0002-8409-1119
Konrad Hoetzenecker https://orcid.org/0000-0001-6775-7460
Alberto Benazzo https://orcid.org/0000-0002-3549-4720
Alex Farr https://orcid.org/0000-0002-4628-9052

REFERENCES

1. Kidd M. Influenza viruses: update on epidemiology, clinical features, treatment and vaccination. Curr Opin Pulm Med. 2014;20(3):242-246.

2. Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiol Rev. 1992;56(1):152-179.

3. Meijer WJ, van Noortwijk AG, Bruinse HW, Wensing AM. Influenza virus infection in pregnancy: a review. Acta Obstet Gynecol Scand. 2015;94(8):797-819.

4. Littauer EQ, Skountzou I. Hormonal regulation of physiology, innate immunity and antibody response to H1N1 influenza virus infection during pregnancy. Front Immunol. 2018;9:2455.

5. Fell DB, Savitz DA, Kramer MS, et al. Maternal influenza and birth outcomes: systematic review of comparative studies. BJOG. 2017;124(1):48-59.

6. Rasmussen SA, Jamieson DJ, Uyeki TM, et al. Extracorporeal membrane oxygenation for adult respiratory failure: life support in the new era. Intensive Care Med. 2012;38(2):210-220.

7. Saad AF, Rahman M, Maybauer DM, et al. Extracorporeal membrane oxygenation in pregnant and postpartum women with H1N1-related acute respiratory distress syndrome: a systematic review and meta-analysis. Obstet Gynecol. 2016;127(2):241-247.

8. Moore SA, Dietl CA, Coleman DM. Extracorporeal life support during pregnancy. J Thorac Cardiovasc Surg. 2016;151(4):1154-1160.

9. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159-2168.

10. Alibrahim OS, Heard CMB. Extracorporeal life support: four decades and counting. Curr Anesthesiol Rep. 2017;7(2):168-182.

11. Taieb A, Jeune F, Lebbah S, et al. Emergency abdominal surgery outcomes of critically ill patients on extracorporeal membrane oxygenation: a case-matched study with a propensity score analysis. World J Surg. 2019;43(6):1474-1482.

12. Yeo HJ, Kim YS, Kim D, Cho WH. Risk factors for complete recovery of adults after weaning from veno-venous extracorporeal membrane oxygenation for severe acute respiratory failure: an analysis from adult patients in the Extracorporeal Life Support Organization registry. J Intensive Care. 2020;8:64.

13. McLaren G, Combes A, Bartlett RH. Contemporary extracorporeal membrane oxygenation for adult respiratory failure: life support in the new era. Intensive Care Med. 2012;38(2):210-220.

14. Hoetzenecker K, Schwarz S, Muckenhuber M, et al. Intraoperative extracorporeal membrane oxygenation and the possibility of post-operative prolongation improve survival in bilateral lung transplantation. J Thorac Cardiovasc Surg. 2018;155(5):2193-2206.e2193.

15. How to cite this article: Foessleitner P, Hoetzenecker K, Benazzo A, et al. Bilateral lung transplantation during pregnancy after ECMO for influenza-A caused ARDS. Am J Transplant. 2021;21:3456–3460. https://doi.org/10.1111/ajt.16781