

Pregnancy and pulmonary hypertension in the pre-lung transplant patient: Successfully saving two lives with extracorporeal lung support

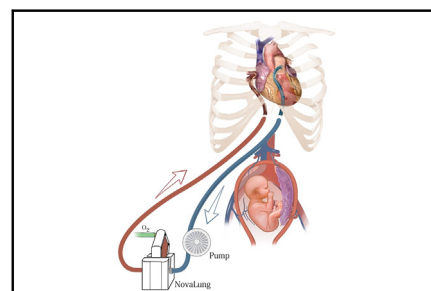


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Lung transplantation (LTx) is the treatment of choice for end-stage lung disease. Patients waiting for LTx have a high 1-year mortality, which increases based on the etiology of the lung failure. Although most patients have a protracted history of lung failure, patients can present late in their disease trajectory or with rapidly progressive disease. Rarely, patients with rapidly progressive lung disease present in pregnancy, which significantly increases the complexity of the situation.

CASE ILLUSTRATION

A 37-year-old female patient (G2P1) presented with a planned pregnancy at 20 weeks of gestation with new dyspnea and hypoxemia. Her previous pregnancy was 12 years earlier, and she was reportedly well until just before presentation. Notably, the patient's mother had a lung transplant for pulmonary hypertension in her early 30s, and her brother died of sudden death in his late 20s. An echocardiogram showed moderate-severe right ventricle (RV) dilation and dysfunction. She was transferred to the University Health Network for further investigations. She underwent a right heart catheterization, which demonstrated a pulmonary artery (PA) pressure of 82/41/54 mm Hg (systolic/diastolic/mean), right atrial pressure 11/8/8 mm Hg, cardiac output 3.19 L/min, pulmonary capillary wedge 9/12/8 mm Hg (C-wave/V-wave/mean), and pulmonary vascular resistance 14.6 Wood units. On repeat echocardiogram, the intraventricular septum was flattened, and the right atrium and



PA-LA ECMO as a bridge to successful delivery and transplant for a pregnant woman with PAH.

CENTRAL MESSAGE

PAH patients can be supported through complex pregnancies with varying ECMO configurations and care from an experienced multidisciplinary team. Sacrifice of the pregnancy may not always be required.

ventricle were severely dilated with moderate-to-severe RV dysfunction. Her computed tomography scan showed no pulmonary embolism, and the lung parenchyma was normal. A ventilation/perfusion scan was not performed, owing to her clinical instability. She had no history of collagen vascular disease or liver disease, and her HIV serology was negative. This clinical presentation in the context of her family history satisfied the diagnosis of heritable pulmonary arterial hypertension (PAH).

At 24 hours following the catheterization, she became profoundly hypoxemic, with oxygen saturations in the 70s. An echo bubble study demonstrated early bubbles consistent with a patent foramen ovale (PFO), likely contributing to her severe hypoxemia. As her main immediate threat to life was felt to be severe hypoxemia, she was placed on venovenous (VV) extracorporeal membrane oxygenation (ECMO) with a femoral drainage cannula and an internal jugular return cannula. The procedure was uncomplicated, with minimal blood loss. This configuration temporarily improved her hypoxemia by providing

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oxygenated blood flow through the PFO. Intravenous epoprostenol and sildenafil were initiated with the hope of treating her PAH and allowing separation from ECMO. Following 2 episodes of profound hypotension early on after VV ECMO initiation, we urgently reconfigured her support to provide more durable hemodynamic stability. At 21 + 5 weeks of gestation, we performed an awake open cannulation of her left femoral artery and placed her on venoarterial (VA) ECMO to allow for induction of general anesthetic. We placed her on a pumpless pulmonary artery to left atrium (PA-LA) circuit using the NovaLung membrane (Xenios AG), to allow for decompression of her RV, circulation of oxygenated blood to the left heart, and potentially allow the reintroduction of medical therapy. We then removed the peripheral VA and VV ECMO and closed her sternotomy. Estimated blood loss was 1 L, and she was transfused 3 units of packed red blood cells during the procedure. She was maintained on intravenous heparin, targeting a partial thromboplastin time of 45 to 60 seconds throughout her ECMO run.

The new diagnosis of PAH in our patient at 20 weeks of gestational age presented a challenging situation for the patient and team. It was felt initially that termination of the pregnancy would be advisable, given the high risk of maternal mortality associated with PAH in pregnancy. Given the gestational age, termination options considered were surgical dilatation and evacuation or medical induction of labor. Both were felt to have a high risk of hemorrhage (associated with anticoagulation) and maternal decompensation. The patient elected to continue the pregnancy, and we felt that the current RV support provided by the PA-LA circuit would possibly provide the opportunity to prolong the pregnancy while mitigating risks to the patient. Our plan for a central PA-LA configuration allowed the opportunity, based on our previous experience, for a safe, durable circuit that could potentially support her for a prolonged period while allowing her to mobilize and potentially have readaptation of the RV and left ventricle.¹⁻³

She remained stable following transition to the PA-LA circuit, with steady flows of 1.3 to 1.6 L, fractional oxygen delivery to the membrane (FDO₂) 1, and sweep 1, and was able to walk up to 100 m with physiotherapy until 25 + 6 weeks of gestational age. She became increasingly hypoxemic to the point that she was unable to mobilize without profound desaturations, likely due to the hemodynamic changes related to pregnancy. In normal pregnancy, maternal blood volume expands by up to 50% by 28 weeks of gestational age, and cardiac output reaches a peak of approximately 30% above prepregnancy levels in the early third trimester, approximately 28 to 32 weeks of gestational age.⁴ A corresponding decrease in systemic vascular resistance occurs during this same period.⁵ These physiological adaptations ensure a low-resistance uteroplacental

circulatory system that permits normal placentation and fetal development and growth. However, in this case these hemodynamic changes likely precipitated the patient's desaturation episodes, as both plasma volume expansion and decreased vascular tone contributed to RV overload and hypotension, respectively. Frequent echocardiograms suggested that the RV was progressively being insufficiently offloaded with the pumpless PA-LA NovaLung. This was compounded by increasing demands of the fetal circuit and ongoing hypotension. As such, we inserted a pump and new oxygenator in her PA-LA circuit to allow for increased flows to improve the off-loading of her RV, essentially providing an RV assist device support (Figure 1). Over the next 3 to 4 weeks, the ECMO flows ranged from 1.6 to 2.2 L, with revolutions per minute of 1700, FDO₂ 1.0, and sweep that weaned from 4 to 2. She remained on epinephrine throughout this time, weaning down to 0.05 µg/kg/min for most of this period. She required one further circuit change for oxygenator failure approximately 4 weeks after pump insertion.

Throughout the course of her treatment, we had regular multidisciplinary meetings with all the relevant specialists: pulmonary hypertension, thoracic surgery, lung transplant, maternal-fetal medicine, obstetrical cardiology, anesthesia, and critical care. We initially counseled the patient that the safest option would be to terminate the pregnancy. The team re-evaluated the options, understanding the patient's wish to continue the pregnancy and following her clinical stabilization on the PA-LA circuit. We considered that pregnancy termination in the second trimester would pose significant risk in and of itself, and that prolonging pregnancy to gain fetal maturity with a planned cesarean delivery and simultaneous or soon-thereafter maternal lung transplantation would be a reasonable approach. With the physiological stabilization of the situation over time and the increasing complexity of termination at the advanced stage of pregnancy, we thus elected to support her through the pregnancy.

However, at 28 + 6 weeks of gestational age, she began to deteriorate, with more desaturations, inability to exercise, and a requirement to increase the ECMO revolutions per minute to 2500 to get flows of 2.6 L to support her. Betamethasone was administered to advance fetal lung maturation, and we proceeded with a cesarean delivery. At the time of the cesarean delivery, the patient was still on PA-LA support. Wires were placed in her femoral vessels in preparation for VA support in case she decompensated on induction of general anesthetic, but she remained stable throughout her delivery. A healthy baby boy (birth weight 1.04 kg) was delivered and attended to by the neonatology team. He was introduced to his mother, who had been extubated shortly after the cesarean delivery (Figure 2). Estimated blood loss was minimal, and she was transfused 1 unit of packed red blood cells during the procedure. After the delivery, the patient remained stable on central PA-LA

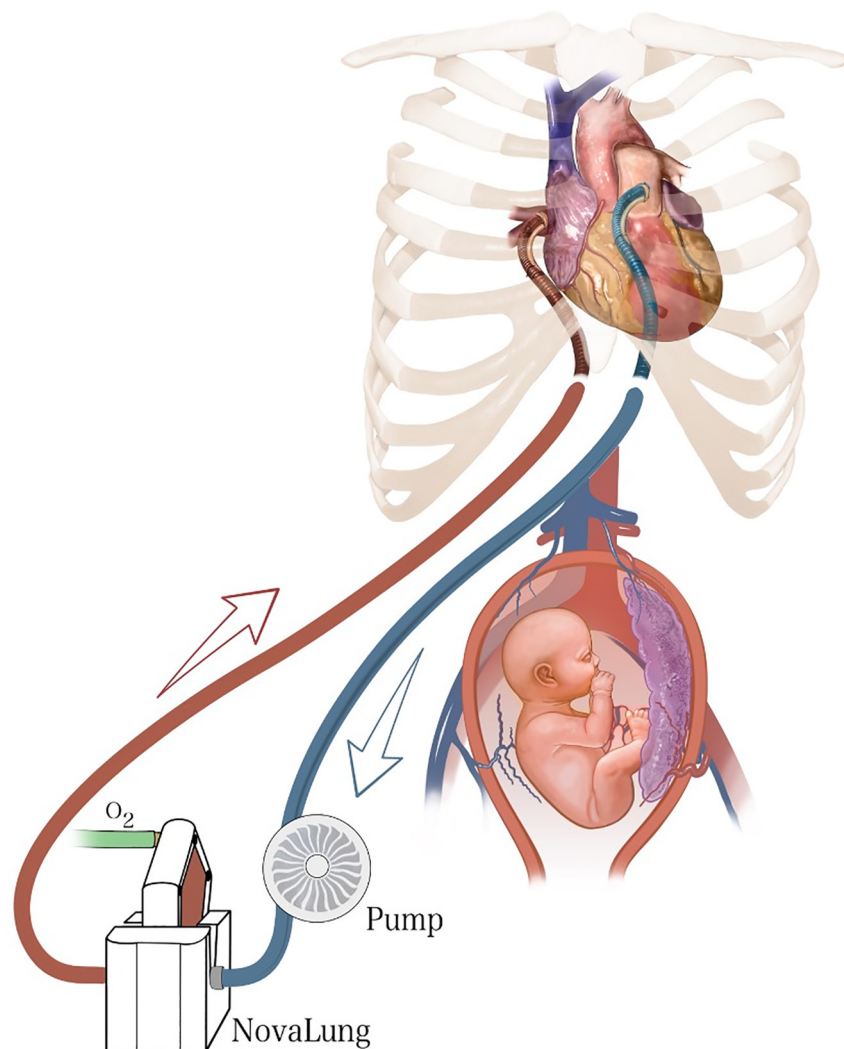


FIGURE 1. Physiology of the mother and fetus with central PA-LA NovaLung with pump in situ. Figure 1 was illustrated by Jay LeVasseur, MFA/Applied Art, LLC. PA-LA, Pulmonary artery to left atrium.

ECMO with pump, with flows ranging from 1.9 to 2.9 L, with revolutions per minute up to 2050, FDO₂ 1.0, and sweep of 2 (Figure 3). She was able to wean off of epinephrine soon after delivery, and 2 weeks' postpartum, she was able to walk a maximum of 30 minutes on the treadmill, after which her exercise tolerance declined. Attempts were made to reintroduce sildenafil and ambrisentan after delivery, yet they had to be held on multiple occasions due to limited per vaginal bleeding post-cesarean delivery and a lower gastrointestinal bleed from an adenomatous polyp just before her transplant.

Three weeks' postpartum, donor lungs became available and due to the inability to make progress with systemic therapy and ongoing RV dysfunction, we felt that the best plan would be to proceed to bilateral lung transplant. During the surgery, we removed the PA-LA circuit and placed

atrial-aortic cannulation for central VA-ECMO, which was discontinued at the end of the surgery. The virtual crossmatch was positive between the patient and donor; thus, she was treated with intraoperative plasma exchange as per our desensitization protocol previously described.⁶ Technically the surgery was challenging but uncomplicated, yet she became increasingly hypoxemic in the early postoperative hours secondary to primary graft dysfunction and required peripheral VV-ECMO. Estimated blood loss was 2 L, and she was transfused 6 units of PRBCs, 2 units of plasma, and 4 units of platelets during the procedure. She was decannulated after 3 days and discharged from hospital 1 month after her transplant (Figure 3). The baby was transferred immediately after birth to the neonatal intensive care unit at the regional tertiary pediatric hospital and was healthy on discharge 12 weeks later, at a corrected



FIGURE 2. Parents meeting the newborn baby after extubation of mom, who remains on central PA-LA NovaLung with pump. PA-LA, Pulmonary artery to left atrium.

gestational age of 41 week. Informed consent was obtained from the patient to discuss her case in detail and share her images. Institutional review board approval was not required.

DISCUSSION

The management of the patient outlined herein required expert multidisciplinary care due to the unique complexities of her situation. Idiopathic PAH is a diagnosis commonly made in young people of child-bearing age. Pregnancy in PAH is a high-risk situation, with a substantial risk of maternal death.^{7,8} Generally, pregnancy is discouraged in this population, yet occasionally patients may choose to proceed with pregnancy despite the medical risk. VA-ECMO and PA-LA NovaLung have been life-saving developments to significantly decrease the waitlist mortality for patients with PAH requiring RV support as a bridge to transplant.⁹ Although peripheral VA-ECMO can be used to

provide adequate hemodynamic support to prevent death, the configuration is nonphysiologic, with increase in left ventricular (LV) afterload that can cause LV distension and pulmonary edema.^{10,11} The use of a PA-LA central circuit with the NovaLung device (Xenios AG) has been an application of ECMO that has the advantage of decompressing the RV with a more physiological configuration, providing the opportunity for prolonged support and RV recovery before lung transplantation.^{3,12} The potential advantage of using the pumpless circuit is that it decreases complications that can occur with the long-term use of a pump (eg, hemolysis, platelet dysfunction).¹³ At our center, nonpregnant patients with PAH who present in right heart failure despite maximal medical therapy are placed on femoral VA-ECMO with transition to central PA-LA NovaLung for RV decompression as a bridge to lung transplant. For patients who do not have adequate RV decompression with this configuration, we change the circuit to PA-LA

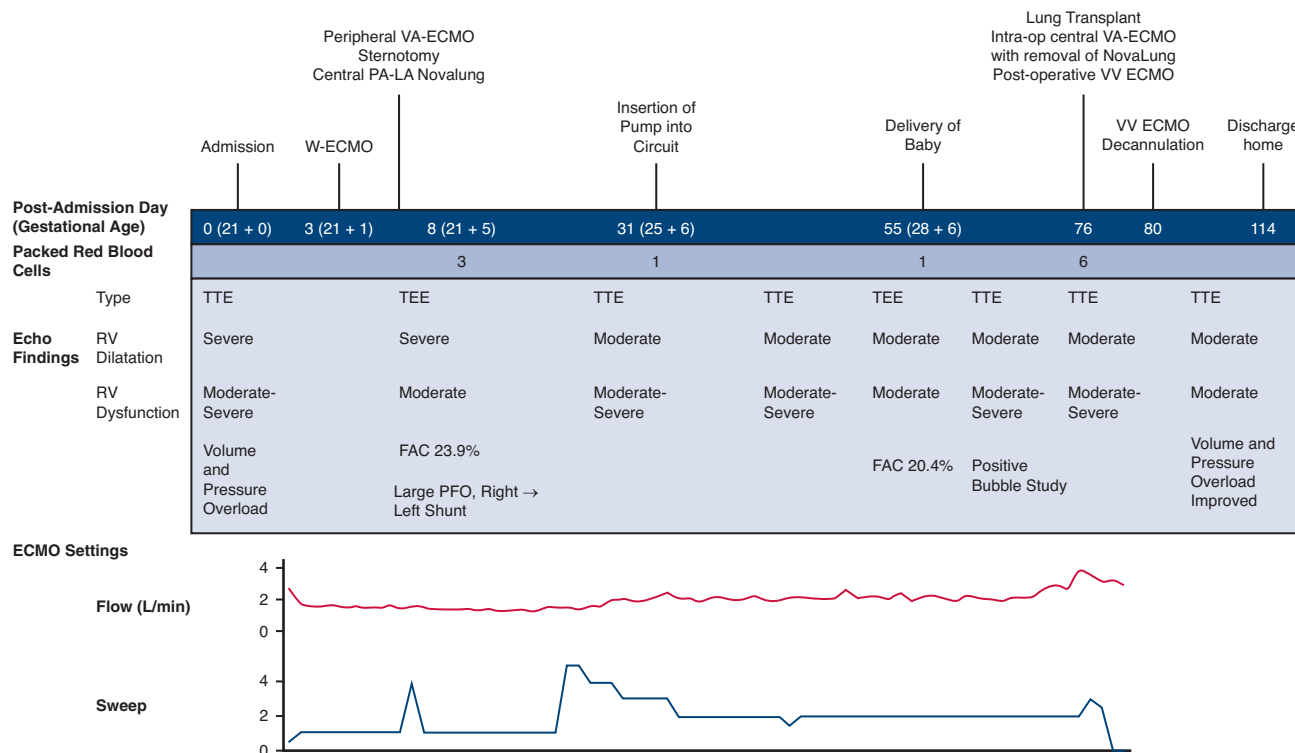


FIGURE 3. Timeline of events throughout the course in hospital. RV, Right ventricle; TTE, transthoracic echocardiogram; VA, venoarterial; PA-LA, pulmonary artery to left atrium; VV, venovenous; ECMO, extracorporeal membrane oxygenation; TEE, transesophageal echocardiogram; FAC, fractional area change; PFO, patent foramen ovale.

ECMO with a pump, which can provide adequate RV off-loading while not increasing LV afterload as with peripheral VA-ECMO. The decision to place this patient on VV-ECMO initially was unique to this situation, in that she was presenting at diagnosis and her main issue was hypoxemia from shunting through her PFO. We felt that providing oxygenation may allow the introduction of medical therapy, and the simpler VV configuration would allow us to start the complex discussions needed around the management of her pregnancy. Although not recommended for most patients, the approach of using VV-ECMO to create an oxygenated shunt in patients with PAH has been described for 3 patients with acute decompensation, with an 87.5% survival to discharge.¹⁴ Also, although there are potential complications with configuration changes, it is important to be able to adapt to the changing needs of the patient. Femoral VA-ECMO is often the most straightforward way to quickly stabilize a patient with PAH who is in extremis as it can be done awake, after which a more definitive configuration can be established.¹⁴

ECMO use in pregnancy for both respiratory and cardiac indications has been shown to have maternal survival rates greater than 70% and, when used in the antepartum period, fetal survival rates of 64.7%.¹⁵ In 2016, Moore and

colleagues¹⁶ published a systematic review of ECMO in pregnancy and found 26 articles describing 45 patients, of which 4 were on VA-ECMO for a mean 15 days. Of these 4 patients, maternal survival was 75% and fetal survival was 25%. In a recent systematic review, 145 patients (40.5%) had VA ECMO in the peripartum period (26 were antepartum) with an average duration of ECMO of 6.9 days.¹⁵ Of the women placed on VV- or VA-ECMO antepartum, there were 35 deliveries, with a maternal survival of 79.4% and fetal survival of 56.3%.¹⁵ Sixteen percent of patients on VA-ECMO developed severe bleeding complications.¹⁵ Since the systematic review there has been a single-center study that reported antepartum ECMO use in 6 patients (2 were peripheral VA-ECMO) with a 100% maternal and fetal survival rate. In this report, 3 of the 6 babies were delivered while the mother was on ECMO, and all were VV configuration at the time of delivery.¹⁷

Recently, the Vienna group reported the first bilateral LTx in a 17-week gestational age woman, which was successful for the mother but resulted in severe intrauterine growth restriction of the fetus and resultant death of the baby 5 days after birth. This patient also experienced severe primary graft dysfunction requiring post-operative VV-ECMO for 3 days.¹⁸

CONCLUSIONS

To the best of our knowledge, this is the first reported case of central PA-LA ECMO use in pregnancy as a bridge to delivery and lung transplantation. Importantly, this provided the opportunity to save both the mother and child with extracorporeal support and a lung transplant. Indeed, it does not have to be assumed that the baby must be sacrificed to save the pregnant mother's life in this predicament. This advanced form of support should be considered for use for pregnant patients with PAH, as it satisfies the physiologic needs of the mother while also potentially allowing for prolonging pregnancy to improve fetal survival. Importantly, this case highlights the need for an interprofessional team approach for very complex patients, with inclusion and prioritization of the values of the patient and her family. This case also demonstrates the importance of managing complex patients such as this in an experienced ECMO and lung transplant center with multidisciplinary consultation and the ability to adapt to the changing needs of the patient and manage multiple circuit configurations and team coordination.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: ECLS, lung transplant, pulmonary arterial hypertension, pregnancy