Case Report

Challenge of Pregnancy in Patients With Pre-Capillary Pulmonary Hypertension: Veno-Arterial Extracorporeal Membrane Oxygenation as an Innovative Support for Delivery

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PULMONARY HYPERTENSION (PH) is a condition characterized by a mean pulmonary arterial pressure ≥ 25 mmHg. PH is defined “pre-capillary” when the pulmonary capillary pressure is < 16 mmHg, and pulmonary vascular resistance is > 3 Wood units. The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines classify PH into 5 groups on the basis of clinical, pathophysiologic, and anatomic criteria.

Patients in group 1 are considered to have pulmonary arterial hypertension (PAH), group 2 has PH due to left-sided heart disease, group has 3 PH due to chronic lung disorders and hypoxemia, group 4 has PH due to chronic thromboembolic disease, and group 5 has PH due to unidentified mechanisms.1

Whatever the cause, PH during pregnancy is associated with an increased risk of maternal (17-28%) and infant (30%) death, given that pregnancy may worsen PH and lead to right ventricular dysfunction. Therefore, the current guidelines recommend avoiding pregnancy in women of childbearing age and affected with PH.2

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Outcomes of pregnant women with PH have improved in recent years due to a better knowledge of the pathophysiology of the disease and to the introduction of new target therapies. Intravenous epoprostenol and inhaled iloprost (prostacyclin and prostacyclin analog) and sildenafil (phosphodiesterase-5 inhibitor) are used successfully during pregnancy while endothelin-receptor antagonists (bosentan, ambrisentan) should be avoided because they are teratogenic.

Outcomes of pregnancy in patients with PAH in the decade 1997 to 2007 was reported to be lower than in the era 1978 to 1996, when no PAH-targeted therapy was available. Mortality was reduced from 30% to 17% in idiopathic PAH, from 36% to 28% in Eisenmenger’s syndrome, and 56% to 33% in PAH of other etiology.

The modern approach to cardiogenic shock takes advantage of extracorporeal circulatory support techniques to overcome the acute ventricular decompensation in those patients in whom a recovery of heart function is expected. Therefore, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) support has been employed increasingly in recent years for a number of different situations requiring right ventricular support as a “bridge to recovery” during acute decompensation.

VA-ECMO enables effective unloading of the right heart chambers, improves the general systemic perfusion, assures adequate oxygenation and carbon dioxide removal, reduces the vasoconstrictive effect of hypoxia, and reduces the effort of breathing in awake patients and the intrathoracic pressures due to high ventilator support. Nonetheless, early postoperative abdominal bleeding can occur even after weaning from ECMO.

The use of ECMO in pregnancy is challenging because of the increased risk of maternal and fetal bleeding or thrombosis, mostly during cesarean section. However, VA-ECMO has been adopted successfully in cases of delivery complicated by left heart decompensation and in patients with a high risk of cardiorespiratory failure.

In this study, the authors describe their experience with the use of VA ECMO for the prevention and management of acute right ventricular failure during delivery in 2 women affected with severe PH. The long-term follow-up also is reported. The report is presented according to the authors’ institutional policy on research publication. Patients gave their consent to anonymous data publication.

### Case Series

**Case 1**

A 31-year-old Caucasian woman affected with thalassemia intermedia requiring regular red blood cell transfusion was referred to the ISMETT PH center because of a suspicion of PH in the 20th week of pregnancy. She presented with lower extremity edema, dyspnea on effort, right ventricle D-shaped enlargement with preserved contractility, an estimated systolic PAP of 70 mmHg, and a World Health Organization Functional Class III (WHO FC III). She recovered rapidly after IV infusion of furosemide, and a right-heart catheterization was scheduled (Table 1). A final diagnosis of moderate precipillary PH associated with chronic hemolytic disease (group V according to the 2015 ESC/ERS guidelines) was established. The patient, despite being informed of all the risks, decided to carry the pregnancy to term. A continuous intravenous infusion of epoprostenol was started and titrated up to 20 ng/kg/min based on the patient’s tolerance and clinical performance. Heparin-based anticoagulation and oral furosemide were maintained throughout the pregnancy. Monthly reassessments were planned, including a 6-minute walking test, pro-BNP, a cardiac ultrasound, and gynecologic and neonatal consultations.

In her 32nd gestational week she was in WHO FC II with regular fetal growth. A regional anesthesia was planned to perform a cesarean section. The patient gave her consent to undergo rescue veno-arterial ECMO during delivery in case of need.

The femoral vein and artery were cannulated preoperatively for eventual rapid exchange in case of the need for ECMO cannulation. An 8-Fr single-lumen introducer was placed in the femoral vein, and an 18-G catheter was placed in the femoral artery.

After the placement of a Swan-Ganz catheter in the pulmonary artery, a subarachnoid anesthesia was given. Four minutes after the incision, vital fetus was extracted (Apgar 7-8-10). A few moments later, during the manipulation of the uterus, sudden hypotension led to cardiac arrest, and the patient was resuscitated with cardiopulmonary resuscitation, intubation, and inhaled nitric oxide. Transesophageal echocardiography (TEE) showed severe right ventricular dilatation and dysfunction. An emergency femoral cannulation was performed through guidewire exchange on the previously placed catheters. After administration of 2500 IU of heparin, an 18-Fr cannula was placed in the femoral vein and a 16-Fr cannula in the femoral artery, reaching a blood flow of 2,000 L/min with a gas

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Group</td>
<td>V (Thalassemia intermedia)</td>
<td>I (congenital porte caval shunt)</td>
</tr>
<tr>
<td>Diagnosis pre-pregnancy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Therapy pre-pregnancy</td>
<td>No</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Therapy during pregnancy</td>
<td>Epoprostenol 20 ng/kg/ min</td>
<td>Sildenafil 20 mg tid</td>
</tr>
<tr>
<td>WHO FC at referral</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>mPAP at referral</td>
<td>33 mmHg</td>
<td>53 mmHg</td>
</tr>
<tr>
<td>Pulmonary capillary pressure</td>
<td>6 mmHg</td>
<td>13 mmHg</td>
</tr>
<tr>
<td>PVR at referral</td>
<td>434 dyne · s · cm⁻⁵</td>
<td>756 dyne · s · cm⁻⁵</td>
</tr>
<tr>
<td>TAPSE</td>
<td>20 mm</td>
<td>21 mm</td>
</tr>
<tr>
<td>Cardiac index at referral</td>
<td>2.8 L/min/m²</td>
<td>2.6 L/min/m²</td>
</tr>
<tr>
<td>WHO FC pre-delivery</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Days on ECMO support</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: ECMO, extracorporeal membrane oxygenation; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistances; TAPSE, tricuspid annular plane systolic excursion; WHO FC, World Health Organization Functional Class.
artery. Soon after, VA-ECMO was started with a blood distal reperfusion cannula (7-Fr) was placed in the femoral (artery 16-Fr and vein 23-Fr) were cannulated surgically, and a mild sedation and under local anesthesia, femoral vessels case, in order to avoid emergency maneuvers during the hours later after a TEE showing no transfered to the intensive care unit. ECMO was removed 24 started to enhance right ventricle contractility. The patient was pulmonary pressure and peripheral perfusion were restored to normal.

Epoprostenol was titrated to 40 ng/kg/min, and dobutamine was started to enhance right ventricle contractility. The patient was transferred to the intensive care unit. ECMO was removed 24 hours later after a TEE showing no fluid overload and a recovered right ventricular function, even with blood flow reduction. The patient was extubated on postoperative day (POD) 5 after weaning of the inhaled NO and dobutamine. During the intensive care unit stay, a progressive decrease of pulmonary vascular resistance (from 500 to 250 dyne·s·cm⁻²), and an increase of cardiac output were observed; the changes in the hemodynamics profile towards a hyperdynamic pulmonary circulation guided the weaning of pulmonary vasodilator agents (nitric oxide and epoprostenol).

The subsequent hospital stay was uneventful, with progressive reduction of systolic pulmonary arterial pressure (sPAP) to 55 mmHg. A CT pulmonary angiogram showed a regular lung parenchyma and no signs of chronic postembolic PH. A lung perfusion scan showed some peripheral defects suggestive of previous distal microemboli. At discharge on POD 15, the patient was in WHO FC II; her cardiac echo showed improved right ventricular dimensions and function, and epoprostenol rate was 20 ng/kg/min.

Over the following 5 months, epoprostenol was down-titrated gradually and switched to oral ambrisentan, 10 mg, + tadalafil, 20 mg. At a 2-year follow-up, the patient was in FC I with no effort limitation.

Case 2

A 31-year-old African woman with a history of PAH with compensated right ventricular (RV) function, and in WHO FC II, treated with sildenafil, became pregnant and came to the authors’ institution in her 4th gestational week. A previous chest CT scan showed aneurysmal dilation of the PA with compression of the right main bronchus. The authors performed a right-CT scan showed aneurysmal dilation of the PA with compression of the right main bronchus. The authors performed a right-heart catheterization, which confirmed a moderate-severe PH. Her baseline hemodynamic parameters are described in Table 1.

The patient was non-compliant with a prostanoid-based treatment. The same follow-up protocol of the previous case was adopted. The patient remained compensated with sildenafil and diuretics throughout her pregnancy until the date of delivery (32nd week), and her baby had regular fetal growth. She was admitted in FC III, and echocardiogram showed a preserved contractility but with signs of initial right ventricular dysfunction and severe dilatation of the pulmonary trunk.

An epoprostenol drip was started at 8 ng/kg/min. Low-flux oxygen supply was added to compensate for mild hypoxemia. In consideration of the authors’ experience with the previous case, in order to avoid emergency maneuvers during the delivery, a pre-emptive ECMO strategy was applied. After mild sedation and under local anesthesia, femoral vessels (artery 16-Fr and vein 23-Fr) were cannulated surgically, and a distal reperfusion cannula (7-Fr) was placed in the femoral artery. Soon after, VA-ECMO was started with a blood flow of 2,000 L/min, a sweep gas flow of 2 L/min, and a 60% F₁O₂.

General anesthesia was induced and a cesarean section performed, resulting in the birth of a healthy baby. No major bleeding was observed, and no blood transfusion was required. The patient was extubated and weaned from ECMO on POD 1 without the need for vasoactive drugs after a weaning trial monitored by TEE.

On POD 3, an urgent re-laparotomy and hysterectomy were performed for abdominal bleeding. This complication, one of the more frequent after cesarean section, occurred 48 hours after the weaning from ECMO and consequently was not thought to relate to the extracorporeal circulation.

Epoprostenol was discontinued 7 days after the delivery. The baby had an uneventful recovery. During the hospital stay, a congenital portocaval shunt was found on a CT scan, suggesting the possibility of a diagnosis of porto-pulmonary hypertension. The patient was discharged on POD 22 in WHO FC II. Macitentan was added to sildenafil. The patient remained in stable FC II for the following year.

Discussion

In cases of PH, pregnancy, with its inherent increased circulating volume and hypercoagulability, results in an unacceptable maternal mortality rate of between 30% and 50%. The authors describe 2 cases of successful pregnancy in women affected with severe pre-capillary PH with a multi-specialist approach, including pulmonologists, cardiologists, anesthesiologists, obstetricians, and neonatologist experts in PH management.

Cesarean section is the preferred way to perform delivery in the case of severe PH. Natural delivery exposes the patient to possible worsening of hypertension and low cardiac and respiratory reserve, results of the effort to cope with the delivery. On the other hand, cesarean section, with its wide blood volume changes, also may expose the patient to risks associated with an already suffering right ventricle.

Moreover, in this setting, the best anesthesia practice is still a matter of debate. In the authors’ series, in the first patient they adopted, at least initially, subarachnoid anesthesia with spontaneous breathing to reduce the negative hemodynamic impact of the increased intrathoracic pressures determined by the positive-pressure ventilation. In the second patient, the authors opted for general anesthesia, also in consideration of the patient’s low compliance with the treatments, because of some linguistic and cultural barriers.

VA-ECMO was effective in obtaining a marked decrease of the right ventricular preload and bypassed the high-pressure pulmonary vascular bed. VA-ECMO enables effective unloading of the right heart chambers, improves the general systemic perfusion, assures an adequate oxygenation and carbon dioxide removal, reduces the vasoconstrictive effect of hypoxia, and reduces the effort of breathing in awake patients and the intrathoracic pressures due to high ventilator support.

In the first patient, VA-ECMO was applied on an emergency basis. In the second patient, it was placed before the abdominal incision (preemptive).
The authors’ limited experience suggests that successful pregnancy can be achieved in patients with advanced pre-capillary PH, after an individualized assessment and preparation of a plan by a multispecialist team with the help of modern circulatory assist devices.\textsuperscript{9,10} However, these results must be confirmed by a larger series before the general recommendation to avoid pregnancy in all patients with PH is reconsidered.

References


