Article

Pulmonary hypertension: Clinical parameters of a difficult case in pregnancy

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Treatment of pulmonary hypertension in pregnancy with a prostacyclin analogue-iloprost and/or calcium channel antagonists appears to improve outcomes and survival. These medications could have been administered to the patient and the response monitored. If the patient did not respond to therapy, this patient may have had either a referral to or transfer to another high risk center with more experience in this type of pregnant patient. There is no literature to support termination of pregnancy improving maternal survival outcomes in these patients, even though termination is recommended by all obstetrical textbooks. Maternal survival, rather, appears to be related to response to therapy, type of therapy, and continuation of therapy.

Summary: A patient who is pregnant with pulmonary hypertension (increased right-sided heart pressures) may be managed with medications. There is no literature to support termination of pregnancy improving maternal survival outcomes in patients with pulmonary hypertension, even though termination is recommended by all obstetrical textbooks. Maternal survival, rather, appears to be related to response to therapy, type of therapy, and continuation of therapy.

Keywords: Pregnancy, Pulmonary hypertension

CASE PRESENTATION

A 27-year-old woman with a history of moderate but well-controlled pulmonary hypertension was seen on October 12, 2009, by her pulmonologist for worsening symptoms of her disease. The results of a routine pregnancy test revealed she was seven-and-a-half weeks pregnant. The pulmonologist counseled that her safest course of action was to end the pregnancy,

since in the best case, pregnancy with pulmonary hypertension carries a 10–15% risk of mortality for a pregnant woman trying to carry to term, and because of the severity of her disease, her own prospects were closer to 50% risk of death. The woman, a Catholic with four children, decided not to terminate.

On November 3, 2009, the woman was admitted to St. Joseph's Hospital and Medical Center with worsening symptoms. At this time, the woman was 11 weeks pregnant. A cardiac catheterization revealed that she now had "very severe

Presented at the 80th Annual Conference of the Catholic Medical Association, Phoenix, AZ, October, 2011.

pulmonary arterial hypertension with profoundly reduced cardiac output”; in another part of the record, a different physician confirmed “severe, life-threatening pulmonary hypertension,” “right heart failure,” and “cardiogenic shock.” The chart noted that she had been informed that her risk of mortality “approaches 100%,” is “near 100%,” and is “close to 100%” if she were to continue the pregnancy. The chart also noted that “surgery is absolutely contraindicated.” The Ethics Committee at St. Joseph’s Hospital and Medical Center was asked for a determination if a D&C would be morally appropriate according to Catholic teaching. Per their reading of the Ethical and Religious Directives for Catholic Health Care Services (4th edition) and their understanding of the Catholic moral tradition, the Ethics Committee determined that the intervention would not be considered a direct abortion. They therefore approved the intervention, which was carried out on November 5, 2009.

INTRODUCTION

Pulmonary arterial hypertension (PAH) has been reported as a rare but significant complication in pregnancy. Idiopathic pulmonary arterial hypertension (IPAH) is a rare condition that has a reported incidence of one or two cases per million per year (Rich et al. 1987). Several noted characteristics of the disease include: vasoconstriction, thrombosis, and vascular proliferation with remodeling. PAH may be idiopathic, as in this patient, or associated with collagen vascular disease, congenital heart disease, portal hypertension, HIV infection, the use of certain medications, and thyroid disorders (Rich et al. 1987). The diagnosis is made hemodynamically with a systolic pulmonary artery pressure >30 mm Hg or a mean pulmonary

arterial pressure of >20 mm Hg (McMillan et al. 2002). Patients with severe IPAH have a previously reported 5-year survival of only 27% with supportive treatment, and a previously reported increased survival rate of 54% with targeted therapy (McMillan et al. 2002). The only known curative therapy for PAH is a heart-lung transplant. Pregnancy with PAH is a morbid condition and carries a serious prognosis. Patients with pre-existing PAH have a high-risk of maternal mortality (30–55%) (Weiss et al. 1998). A systematic review by Bedard, Dimopoulos, and Gatzoulis (2009), found a somewhat decreased overall mortality rate of 28%, and with idiopathic pulmonary hypertension, as in this patient, a lower (17%) mortality in their review.

A review of the literature by Archer and Michelakis in 2006 found several classes of medications and various means of administration that may be useful in the treatment of PAH. These included: calcium antagonists, prostaglandin analogs, endothelin antagonists, and phosphodiesterase-5 inhibitors (Archer and Michelakis 2006).

The use of calcium antagonists in PAH lies in their clinical effects in responding patients. Rich, Kaufmann, and Levy (1992) in a non-randomized study of 64 patients, found that 26% of their PAH patients responded to high-dose calcium antagonists with a decrease in PVR by 20% or more. The 5-year survival rates were significantly increased in the responders (97% versus 55%) (Rich et al. 1992). The limitations to calcium agonist therapy are that many of the PAH patients will not respond to this therapy acutely, and, symptomatic hypotension and edema limit this therapy. The endothelium of the PAH patient is thought to be deficient in production of prostacyclin and thus the use of prostacyclin analogs (Barst et al. 1996). Epoprostenal, a prostacyclin

analog, has a half-life of about 3 minutes and must be given intravenously. The side effects that may limit therapy are related to the vasodilatory properties of the drug and include: jaw pain, flushing, headache, diarrhea, erythematous rash, and leg pain. Tachyphylaxis is common and the dosages must be adjusted frequently. Epoprostenol is the only drug shown to improve survival in PAH (McLaughlin, Shillington, and Rich 2002).

Phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil) increase the effects of both the brain natriuretic peptide and nitric oxide (NO), increase cGMP, and promote vasodilatory and antiproliferative effects in the pulmonary circulation. Sildenafil (50–100 mg tid) has been shown in small trials and case reports to have as selective and effective results as inhaled NO in patients when given in acute treatment for PAH (Michelakis et al. 2002). Main side effects of the therapy are flushing, diarrhea, and heartburn. Sildenafil, due to its effectiveness, convenience in dosing, and cost, may be one of the best first line therapies in PAH patients, especially the NYHA Class III patients.

RECENT PREGNANCY CARE

A case series by Elliott et al. (2005) of three pregnant patients treated with iloprost found that treatment with the prostacyclin analog (iloprost) allowed the patients to reach 25, 36, and 35 weeks gestation for delivery. Iloprost is a prostacyclin analog with a half-life of about 25 minutes with the major advantage that it may be administered by inhalation. It has been approved for treatment of PAH in both Europe and the United States. The drug is administered in multiple 5-minute sessions (6–9 times/day) using ultrasonic nebulizers (Gessler et al. 2001). The use of airway nebulization delivers the iloprost

directly to the pulmonary arteries with little systemic effects. Two previous open-label studies of iloprost in PAH for 3 months and 1 year as well as a 3-month double-blinded, placebo-controlled, randomized-controlled study verified the efficacy of the therapy (Hoepfer, Schwarze, and Ehlerding 2000; Olschewski et al. 2000). Iloprost is generally administered six to nine times a day at 2.5 or 5 µg for a total dosing of 45 µg/day.

Treatment of all three patients was with nebulized iloprost from as early as 8–17 weeks at initiation of therapy (Elliot et al. 2005). Therapeutic low molecular weight heparin (LMWH) was also added to the patients' 1 & 2 (without the previous) therapeutic regimen for anticoagulation and to prevent pulmonary embolism in these high risk patients (Elliot et al. 2005).

The most recent data from Kiely et al. (2009), not available as published data in 2009, presents a much improved survival rate with the implementation of a multi-professional approach to care. Kiely et al. (2009) managed nine women from April 2002 to April 2009 with targeted therapy. Four of the women had new onset PAH in pregnancy (24–33 weeks of onset), the other five had been previously diagnosed (6–24 weeks at onset of care). The management of these women consisted of four to seven doses of iloprost per day. Patients 1–3 received 10–20 µg/dose with the ultrasonic nebulizer and patients 4–9 received 5 µg via an INeb. Intravenous therapy with iloprost was needed in two patients. LMWH was used in all nine women (five with full anticoagulation and four with prophylactic dosing). Eight of the nine deliveries were by cesarean section with either spinal or epidural anesthesia. There was use of radial arterial and internal jugular central lines in the cases to manage central pressures. Swan-Ganz catheters were used to obtain thermodilution measurements of cardiac output. This

series resulted in all nine patients delivering a live born baby and there were no maternal mortalities in any of the nine patients postpartum. All women were alive at the time of the article with a median follow up of >3 years (range 0.8–6.5 years). Five of the women were able to transition to oral therapy from the nebulized treatment. The success of this approach depended on the close cooperation of pulmonary vascular physicians, nurses, obstetricians, maternal-fetal medicine specialists, anesthesiology, and hematologists (Kiely et al. 2009).

At the time of the patient's presentation in 2009, there was sufficient data available on treatment of patients with a prostacyclin analog iloprost and/or calcium channel antagonists. These medications could have been administered to the patient and the response monitored. If the patient did not respond to therapy, this patient may have had either a referral to or transfer to another high risk center with more experience in this type of pregnant patient. There is no literature to support termination of pregnancy improving maternal survival outcomes in these patients, even though termination is recommended by all obstetrical textbooks. Maternal survival, rather, appears to be related to response to therapy, type of therapy, and continuation of therapy.

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BIOGRAPHICAL NOTE

Dr. Calhoun serves as Professor and Vice Chair in the Department of Obstetrics and Gynecology at West Virginia University-Charleston and is directly involved in resident and medical student education. He is a diplomate of the American Board of Obstetrics and Gynecology with board certification in general Obstetrics and Gynecology, in the sub-specialty of Maternal-Fetal Medicine, and is also board certified in Addictions Medicine.