

## THE PREGNANT PATIENT WITH PULMONARY ARTERY HYPERTENSION

### - A Review -

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#### Introduction

The first international conference on pulmonary hypertension was organized by the World Health Organization in 1973. At that time there were no effective therapies and patients with primary or idiopathic pulmonary hypertension had a median survival of less than 3 years. Now many treatments have more than doubled the survival time and more patients present for surgery and anesthesia and survive to become pregnant. Nevertheless, pregnancy complicated by pulmonary hypertension poses risks to the mother that can prove fatal. Two recent articles have outlined the current treatment modalities and the management of pulmonary hypertension during pregnancy<sup>1,2</sup>.

#### Classification of Pulmonary Hypertension

Pulmonary hypertension (PH) is an increase in pressure in the pulmonary artery, vein or capillaries (lung vasculature), leading to dyspnea, dizziness, fainting, and other symptoms, all of which are exacerbated by exertion. Pulmonary hypertension can be a severe disease with a markedly decreased exercise tolerance and heart failure. First identified by Dr. Ernst von Romberg in 1891<sup>3</sup>, pulmonary hypertension was previously divided into 2 categories: primary pulmonary hypertension and secondary pulmonary hypertension, based on identifiable etiology. In 1998, the World Health Organization (WHO) proposed a clinical classification of pulmonary hypertension based on similarities in pathophysiology, clinical presentation, and therapeutic options, classifying PH to one of five different types<sup>4</sup>: arterial, venous, hypoxic, thromboembolic or miscellaneous.

As noted above, the 1973 meeting organized by the World Health Organization was the first to attempt classification of pulmonary hypertension. A distinction was made between primary and secondary PH, and primary PH was divided to the "arterial plexiform", "veno-occlusive" and "thromboembolic" forms. A second conference in 1998 at Évian-les-Bains also addressed the causes of secondary PH (i.e. those due to other medical conditions), and in 2003, the 3rd World Symposium on Pulmonary Arterial Hypertension was convened in Venice to modify the classification based on new understandings of disease mechanisms. The revised system developed by this group provides the current framework for understanding pulmonary hypertension. The system includes several improvements over the former 1998 Evian Classification system. Risk factor descriptions were updated, and the classification of congenital systemic-to pulmonary shunts was revised. A new classification of genetic factors in PH was recommended, but not implemented because available data were judged to be inadequate<sup>4</sup>.

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The Venice 2003 Revised Classification system can be summarized as follows:

- Group I - Pulmonary arterial hypertension (PAH)
  - Idiopathic (IPAH)
  - Familial (FPAH)
  - Associated with other diseases (APAH): collagen vascular disease (e.g. scleroderma), congenital shunts between the systemic and pulmonary circulation, portal hypertension, HIV infection, drugs, toxins, or other diseases or disorders
  - Associated with venous or capillary disease
- Group II - Pulmonary hypertension associated with left heart disease
  - Atrial or ventricular disease
  - Valvular disease (e.g. mitral stenosis)
- Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia
  - Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD)
  - Sleep-disordered breathing, alveolar hypoventilation
  - Chronic exposure to high altitude
  - Developmental lung abnormalities
- Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
  - Pulmonary embolism in the proximal or distal pulmonary arteries
  - Embolization of other matter, such as tumor cells or parasites
- Group V Miscellaneous. Pulmonary hypertension due to the direct effect on the pulmonary vasculature of inflammatory diseases such as schistosomiasis, sarcoidosis, histiocytosis X, and fibrosing mediastinitis.

The classification does not include sickle cell disease, which may also cause PH. Also, Human herpes virus 8, also associated with Kaposi's sarcoma, has been demonstrated in patients with PAH, suggesting that this virus may play a role in its development. An association between human herpesvirus 8 and idiopathic pulmonary arterial hypertension (IPAH) remains controversial.

## Pathogenesis

Whatever the initial cause, pulmonary arterial hypertension (WHO Group I) involves the vasoconstriction of blood vessels connected to and within the lungs increasing cardiac load. Over time, the affected blood vessels fibrose, further increasing pressure within the lungs and impairing blood flow. The right ventricular hypertrophies (cor pulmonale develops), decreasing the ability of the heart to pump blood through the lungs, ultimately causing right heart failure. As blood flow through the lungs decreases, the left side of the heart receives not only less blood but also poorly oxygenated blood, decreasing the ability to supply sufficient oxygen to the rest of the body, especially during physical activity.

Pathogenesis in pulmonary venous hypertension (WHO Group II) differs in that there is no obstruction to

blood flow in the lungs. Instead, the left heart fails to pump blood efficiently, leading to pooling of blood in the lungs causing pulmonary edema and pleural effusions.

In hypoxic pulmonary hypertension (WHO Group III), the low levels of oxygen are thought to cause vasoconstriction of pulmonary arteries leading to a pathophysiology similar to pulmonary arterial hypertension.

In chronic thromboembolic pulmonary hypertension (WHO Group IV), vessels are blocked or narrowed with blood clots. Again, the pathology is similar to that seen in pulmonary arterial hypertension.

A further classification is made on functional ability. These classes are based on information adapted from the executive summary of the world symposium on Primary Pulmonary Hypertension in Evian, France in 1998.

- Class I: These are patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
- Class II: These are patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- Class III: These are patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- Class IV: These are patients with pulmonary hypertension with an inability to perform any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

## Epidemiology

The overall prevalence of pulmonary hypertension in the general population is unknown, owing to the heterogeneity of the disease. In specific subgroups of pulmonary hypertension patients, studies have estimated the prevalence as follows:

- In an observational study of 277 patients with HIV infection, 46% of patients had pulmonary hypertension. In comparison with prior studies, no change in prevalence rate was seen with modern highly active antiretroviral treatment (HAART)<sup>6</sup>.
- A systematic review of several studies of patients with obstructive sleep apnea (OSA) estimated the prevalence of pulmonary hypertension at 15-20%<sup>7</sup>.
- A systematic review of several studies among patients with chronic obstructive pulmonary disease (COPD) estimated the prevalence of pulmonary hypertension at 10-30%<sup>8</sup>.
- In scleroderma patients, the incidence has been estimated to be 6-60% of all patients, with the variance based on the extent of disease<sup>9</sup>.
- In patients who took the diet medication fenfluramine/phentermine, there was a 23x increase in the development of PH, often long after ingestion of the drug combination.

Regarding mortality and morbidity for patients with PH and based on the US Centers for Disease Control and Prevention (CDC) Pulmonary Hypertension Surveillance from 1980-2002, the following were reported<sup>10</sup>:

- The age-standardized death rates for the total US population increased from 5.2 deaths to 5.4 deaths per

100,000 population.

- The main increase in death rates was seen among women, with 3.3 deaths to 5.5 deaths per 100,000 population, and blacks, with 4.6 deaths to 7.3 deaths per 100,000 population.
- The death rate in males decreased over this time, from 8.2 deaths to 5.4 deaths per 100,000 population.

## Diagnosis

Because of the many etiologies of PH a series of tests must be performed to distinguish pulmonary arterial hypertension from *venous, hypoxic, thromboembolic, or miscellaneous* varieties.

A physical examination looks for typical signs of pulmonary hypertension including altered heart sounds, such as a widely split S<sub>2</sub> or second heart sound, a loud P<sub>2</sub> or pulmonic valve closure sound (part of the second heart sound), (para)sternal heave, possible S<sub>3</sub> or third heart sound, and pulmonary regurgitation. Other signs include an elevated jugular venous pressure, peripheral edema, ascites, hepatojugular reflux, and clubbing.

Further procedures are required to confirm the presence of pulmonary hypertension and exclude other possible diagnoses. These generally include pulmonary function tests; blood tests to exclude HIV, autoimmune diseases, and liver disease; electrocardiography (ECG); arterial blood gas measurements; X-rays of the chest (followed by high-resolution CT scanning if interstitial lung disease is suspected); and ventilation-perfusion or V/Q scanning to exclude chronic thromboembolic pulmonary hypertension. Thoracic echocardiography (TTE) is used widely as a screening tool for PH. There is good correlation between PA pressures and right ventricular systolic pressure. However, several factors such as severe lung disease, premature ventricular contractions, and inaccurate estimates of right atrial pressure can lead to misdiagnosis. Studies have found that TTE may overestimate PA pressures when compared with right heart catheterization (RHC)<sup>2</sup>. On the other hand, in about one third of patients, RHC may reveal more severe PH than is estimated from TTE. Thus both under and over estimating may occur. However, PH does not mean PAH is present and thus assessment of PA occlusion pressures and PVR must be made. In fact, the diagnosis of PAH must be made confirmed with RHC in pregnant patients, given the high morbidity and mortality associated with the combination of the two conditions. Biopsy of the lung is usually not indicated unless the pulmonary hypertension is thought to be due to an underlying interstitial lung disease. Lung biopsies carry risks of bleeding due to the high intrapulmonary blood pressure. Clinical improvement is often measured by a "six-minute walk test", i.e. the distance a patient can walk in six minutes. Stability and improvement in this measurement correlate with better survival. Brain natriuretic peptide levels (BNP) may be used to follow the progress of patients with pulmonary hypertension.

Although pulmonary arterial pressure can be estimated on the basis of echocardiography, pressure measurements with a pulmonary artery (PA) catheter provides the best assessment. PAOP and PVR cannot be measured directly by echocardiography. Therefore diagnosis of PAH requires right-sided cardiac catheterization. A PA catheter can also measure cardiac output, which is more important in measuring disease severity than pulmonary arterial pressure. Diagnosis of PAH requires the presence of pulmonary hypertension with two other conditions. Pulmonary artery occlusion pressure (PAOP or PCWP) must be less than 15 mm Hg (2000 Pa) and pulmonary vascular resistance (PVR) must be greater than 3 Wood units (240 dyn•s•cm<sup>-5</sup> or 2.4 mN•s•cm<sup>-5</sup>). Normal pulmonary arterial pressure in a person at sea level has a mean value of 12–16 mmHg (1600–2100 Pa). Pulmonary hypertension is present when mean pulmonary artery pressure exceeds 25 mmHg (3300 Pa) at rest or 30 mmHg (4000 Pa) with exercise. Mean pulmonary artery pressure (mPAP) should not be

confused with systolic pulmonary artery pressure (sPAP), which is often reported on echocardiogram reports. A systolic pressure of 40 mm Hg typically implies a mean pressure of more than 25 mmHg. Roughly,  $mPAP = 0.61 \cdot sPAP + 2$ .

### Physiologic Changes of Pregnancy

There are several cardiopulmonary physiologic changes with pregnancy that exacerbate PH. In the pulmonary system, minute ventilation increases by 50% at term. Arterial carbon dioxide decreases to about 34mmhg. Functional residual capacity, expiratory reserve volume and residual volume all decrease. Total lung capacity remains the same because of increase in chest circumference. The smooth muscle relaxation effects of progesterone may decrease airway resistance and improve function. Cardiac changes include a 50% increase in cardiac output, with early increases in blood volume that lead to increased stroke volume. Afterload is reduced secondary to decreased peripheral vascular resistance. Later, cardiac output is augmented by tachycardia. Normally, pulmonary vascular resistance (PVR) decreases to allow for these changes, an accommodation that is not possible in patients with PH. As afterload increases from the higher PVR, the right ventricle cannot handle the increased cardiac output and begins to fail. Sudden death from dysrhythmia may occur. Peak plasma volumes develop about 22-24 weeks and cardiac output peaks around 32 weeks.

At the time of delivery, pain stimulates the sympathetic nervous system with sudden significant increases in heart rate, blood pressure and myocardial oxygen consumption. Vagal responses may also occur and lead to hypotension and sudden death<sup>11</sup>. Valsalva maneuvers may further increase blood pressure and myocardial oxygen consumption. Also, with each uterine contraction, about 500ml blood is pushed into the maternal circulation. After delivery, autotransfusion from the uterine circulation and increased venous return from the relief of inferior vena cava pressure cause large fluid shifts to the maternal circulation. Right ventricular volume overload can occur easily.

Pregnancy is associated with a hypercoagulable state due to increased fibrin levels, reduced fibrinolytic activity, increased procoagulant activity with higher resistance to activated protein C, lower protein S, and increased clotting factor activity<sup>12</sup>. Any degree of thromboembolism contributes to a poor outcome in pregnant patients with PH.

### Pulmonary Hypertension and Pregnancy

Pulmonary hypertension affects a relatively small number of pregnancies (approximately 0.0003%)<sup>13</sup>. However, mortality is reported as high as 60% in older studies<sup>2</sup>. More recent studies indicate a decline in mortality to around 25%, with patients in the IPAH group showing the most improvement (17%), perhaps due to the incorporation of PAH specific therapy which is more likely to be used for patients with IPAH<sup>14</sup>.

Previously undiagnosed PH may manifest first with the stress of pregnancy. It can also develop acutely during pregnancy. Sudden onset of dyspnea, syncope or chest pain should be immediately investigated. Differential diagnosis includes: sleep apnea, asthma, arteriovenous malformations, atrial myxoma, amniotic fluid embolism, atrial septal defect, cardiomyopathy (dilated, hypertrophic or restrictive), chronic obstructive pulmonary disease, emphysema, mitral regurgitation and stenosis, restrictive and interstitial lung disease and systemic lupus erythematosus.

As soon as a diagnosis of PH is made, patients should be followed with regular assessment of RV function with TTE. Should dysfunction be detected, early delivery is recommended<sup>2</sup>. While no anesthetic technique has proven superior, most patients were delivered in the few studies reported under spinal or epidural anesthesia<sup>2</sup>. Of note is that during delivery, hypotension may develop from the several medications used to treat PH including oxytocin, pulmonary vasodilator drugs, inotropes (dobutamine) and analgetics. Vasopressin preferentially increases systemic vascular resistance without increasing PVR and is a viable option to support blood pressure without compromising RV function. Maternal death is most likely to occur in the postpartum period when maximum fluid shifts occur.

## Treatment

While there is no curative therapy short of lung transplantation, several treatments have shown promise in improving outcome for patients with PH. Therapy is dictated in part by the cause, whether it be arterial, venous, hypoxic, thromboembolic, or other. Since pulmonary venous hypertension is synonymous with congestive heart failure, the treatment is to optimize left ventricular function by the use of diuretics, beta blockers, ACE inhibitors, etc., or to repair/replace the mitral valve or aortic valve. Digoxin, diuretics, and oxygen have been advocated but results are inconsistent. High dose calcium channel blockers are useful in only 5% of IPAH patients who are *vasoreactive* by pulmonary artery catheter measurements. Unfortunately, calcium channel blockers have been largely misused, being prescribed to many patients with non-vasoreactive PAH, leading to excess morbidity and mortality. The criteria for vasoreactivity have changed. Only those patients whose *mean* pulmonary artery pressure falls by more than 10 mm Hg to less than 40 mmHg with an unchanged or increased cardiac output when challenged with adenosine, epoprostenol, or nitric oxide are considered vasoreactive.<sup>15</sup> Of these, only half are responsive to calcium channel blockers in the long term<sup>16</sup>. Several agents have recently been introduced for primary and secondary PAH. The trials supporting the use of these agents have been relatively small, and the only measure consistently used to compare their effectivity is the "6 minute walking test". Many have no data on mortality, benefit or time to progression<sup>17</sup>.

RV failure is the most common cause of death in pregnant patients with PH. Thus therapy has aimed at reducing PVR. Three of the many vasoactive pathways involved in the abnormal proliferation and contraction of the smooth muscle cells of the pulmonary arteries have been targeted with drugs - endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives. Prostacyclin (prostaglandin I<sub>2</sub>) is commonly considered the most effective treatment for PAH. Epoprostenol (synthetic prostacyclin, marketed as Flolan) is given via continuous infusion that requires a semi-permanent central venous catheter. This delivery system can cause sepsis and thrombosis. Flolan® is unstable, and therefore has to be kept cold during administration. Since it has a half-life of 3 to 5 minutes, the infusion has to be continuous (24/7), and interruption can be fatal. Other prostanoids have therefore been developed. Treprostinil (Remodulin®) can be given intravenously or subcutaneously, but the subcutaneous injection can be very painful. An increased risk of sepsis with intravenous Remodulin has been reported by the CDC. Iloprost (Ilomedin®) is also used in Europe intravenously and has a longer half life. Iloprost (marketed as Ventavis®) was the only inhaled form of prostacyclin approved for use in the US and Europe, until the inhaled form of treprostinil was approved by the FDA in July 2009 and is marketed under the trade name Tyvaso®. The inhaled form of administration has the advantage of selective deposition in the lungs with less systemic side effects, however coughing and throat irritation commonly occur. Oral and inhaled forms of Remodulin® are under development. Beraprost is an oral

prostanoid available in South Korea and Japan.

The dual (ET<sub>A</sub> and ET<sub>B</sub>) endothelin receptor antagonist bosentan (marketed as Tracleer®) was approved in 2001. Sitaxentan, a selective endothelin receptor antagonist that blocks only the action of ET<sub>A</sub>, has been approved for use in Canada, Australia, and the European Union, marketed under the name Thelin®. It has not been approved for marketing by the U.S. Food and Drug Administration (FDA). In 2010, Thelin® was withdrawn by Pfizer due to severe side effects. A new trial to address the FDA's concerns began in 2008. A similar drug, ambrisentan is marketed as Letairis® in U.S. (Gilead Sciences). In addition, another dual/nonselective endothelin antagonist, Actelion-1, from the makers of Tracleer®, entered clinical trials in 2008.

Sildenafil, a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), was approved for the treatment of PAH in 2005, marketed as Revatio®. In 2009, tadalafil, another PDE5 inhibitor, marketed under the name Adcirca® or Cialis® was also approved.

The nitric oxide (NO) signaling pathway is important for many physiological functions including vascular smooth muscle relaxation, neuronal signal transduction and inhibition of platelet aggregation. The source of NO in vivo is the enzyme **nitric oxide synthase**. The principal receptor for NO is soluble guanylate cyclase (sGC). Several sGC activators including cinaciguat and **riociguat** are undergoing clinical trials for the treatment of PAH.

There is conflicting data as to the fetal effects of these medications. However, at least anecdotal reports indicate safe usage with most of them<sup>2</sup>.

Several surgical procedures have been described for the treatment of PH. **Atrial septostomy** creates a communication between the right and left **atria** and relieves pressure on the right side of the heart, but at the cost of relative hypoxia. **Lung transplantation** cures pulmonary arterial hypertension, but leaves the patient with the complications of transplantation, and a post-surgical **median** survival of just over five years<sup>18</sup>. **Pulmonary thromboendarterectomy** (PTE) is a difficult, major procedure that is currently performed in a few select centers but with apparent good success in select patients.

## Management of a Typical Case

A 39 year old woman, approximately 18 weeks pregnant presented to the emergency room complaining of excessive tiredness, dyspnea, syncope and ankle swelling. She had never had surgery and this was her first pregnancy. To date she had had no prenatal care. She reported taking several multivitamin preparations and some herbals. Several years before she was told that she had a heart murmur. On physical examination she weighed 215lbs and was 64in tall. There was slight cyanosis of her lips and marked swelling of her feet and ankles. On auscultation, split S2 and loud P2 sounds were heard. BP 155/95, Heart rate 101 with frequent PVC's, spO2 92 on room air. Hct 29%, blood sugar, 189mg/dl.

A diagnosis of pulmonary artery hypertension was made and she was tentatively scheduled for termination of pregnancy. Anesthetic consultation was sought.

Right heart catheterization indicated that the patient had severe pulmonary hypertension (WHO Group IV). Further evaluation determined that she had sarcoidosis. She was counseled as to continuation of the pregnancy. Given her obesity and gestational diabetes and the established right heart dysfunction it was agreed that late termination would be the safer choice with steroid therapy for the treatment of sarcoid. The patient was

reluctant to agree as this was her first and perhaps only, pregnancy. She was given further opportunity to discuss the situation and to review the available data with a team of obstetricians, cardiologists, pulmonologists and anesthesiologists with input from psychologists and social workers. She acknowledged that the chances of her survival and that of the baby were less than 50% and she agreed to proceed with termination. A course of prednisone and high dose calcium channel blockers was started.

Decision was made to perform the termination in an operating room prepared for open heart surgery. A cardiac surgeon was placed on stand by as was the entire team. Anxiolysis was achieved with midazolam 4mg. The radial artery was cannulated and a pulmonary artery catheter placed. After antacid prophylaxis, caudal analgesia was achieved. Vasopressin was prepared but was not required. Evacuation was completed in 12 minutes. Oxytocin was withheld because of the theoretical risk of increase of PVR. The patient was transferred to the ICU and carefully observed for 24 hours. She was then discharged for further evaluation prior to mitral valve replacement.

## **Conclusion**

Pulmonary hypertension complicating pregnancy carries serious considerations for anesthetic management. As the pregnancy progresses, the risk of sudden death increases. Diagnosis as to the cause of the pulmonary hypertension is essential. Close communication with cardiology, pulmonology and obstetrical teams are essential. Psychological support for the patient is also indicated as termination is frequently the safer route for the mother.

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