Pulmonary Arterial Hypertension in Pregnancy

“The Perfect Storm”

SC Zungu

Moderator: C Van den Bosch
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Introduction

A perfect storm is an event in which a rare combination of circumstance drastically aggravates the event. The term is taken from analogy to an unusually severe storm that results from a rare combination of meteorological phenomena. In medicine there are rare situations where very bad combination of disease process occur at the same time and pregnancy in pulmonary hypertensive patients is that “perfect storm”.

Pulmonary hypertension is a condition characterised by elevated pulmonary arterial pressure (PAH) and secondary right heart failure.\(^1\) PAH is a rare and devastating disease characterised by pulmonary vascular remodeling that limits the ability of the pulmonary vascular bed to withstand the physiological changes of pregnancy.\(^2\) Women are affected 3-4 times more commonly than men, majority being of childbearing age, resulting in an increase interest on the mechanistic role of sex hormones in pulmonary vascular disease.\(^3\)

The PH in pregnancy is known to be associated with significant high mortality rate between 30% and 56 % but decreasing in recent reviews (16% and 30%).\(^4, 5\) The change is attributed to the availability of new targeted treatment and the use of a team based, multidisciplinary approach.\(^6\) The mortality rate of women with Eisenmenger’s syndrome is 20-50%. The foetus unfortunately, is also at high risk for growth restriction, preterm delivery and perinatal mortality.\(^7\)

Most literature and guidelines still advocate for women of childbearing age with PH not to fall pregnant, or terminate a pregnancy early depending on the severity of the disease.\(^8, 9\) Some women are diagnosed late and some despite the risks to both mother and foetus, will decide to continue with the pregnancy.\(^9\) Hence, a thorough understanding of how PH affects pregnancy and how it is managed is essential for the anaesthesiologist caring for these patients.

A multidisciplinary team approach is crucial to achieve successful outcomes in these difficult cases.\(^9\) The role of the anaesthesiologist is crucial for the successful outcomes in this patient population. Hence, this review will be looking at the approach to a pregnant patient with pulmonary hypertension focusing on the role of an anaesthesiologist in the multidisciplinary team environment.

Definition and Classification

PH was defined as mean pulmonary artery pressure (mPAP) ≥25 mmHg as assessed by right heart catheterization (RHC) during the first World Symposium on Pulmonary Hypertension (WSPH) in October 1973 in Geneva.\(^9\) During the 6th WSPH in Nice the haemodynamic definition of PH was changed to mPAP of ≥20 mmHg, due to the fact that the original definition did not represent the upper limit of normal mPAP in the general population. The normal mPAP in healthy individuals is approximately 14 ± 3.3 mmHg and the upper limit of normal is 20 mmHg.\(^10\) They were definite concerns about diagnosing PH in otherwise healthy individuals with mPAP between 21 and 24 mmHg, but the evidence from studies published in the last 5 years suggest that patients with
mPAP of 21 to 24 mmHg are at increased risk of poor outcomes and usually progress to “overt PH more often than patients with mPAP of less than 20 mmHg when followed up over 2-3 years.”\(^{(10)}\) There is lack of evidence to define which level of exercise-induced changes in mPAP or PVR have prognostic implications, as such a disease entity ‘PH on exercise’ should not be used.\(^{(11)}\) The severity grading of pulmonary hypertension (mPAP) of mild (20-40 mmHg), moderate (41-55 mmHg) and severe (≥ 55mmHg) is not used by most authors. In (table 3) the summary of the 2015 ESC/ERS guidelines which uses clinical signs and symptoms, WHO functional classification, 6MWD and other measurements to categorize patients as low, intermediate or high risk.\(^{(12)}\)

The WHO differentiates 5 major groups of pulmonary hypertensive disorders that differ in their pathogenesis, severity, structural abnormalities, prognosis and treatment strategies (Table 1). PH patients associated with left heart disease (Group 2) are characterised by pulmonary wedge pressures > 15 mmHg, or post-capillary PH, while all other groups have pre-capillary PH with pressures < 15 mmHg.\(^{(8)}\) PAH (Group 1) is characterised by the presence of pre-capillary PH and PVR > 3 Wood units, in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases.\(^{(11)}\)
The 6th WSPH updated haemodynamic definition of PH as shown in Table 2. The haemodynamic profiles have been reduced to three (mPAP, PCWP, and PVR). The previous definition comprised of various combinations of PAP, PAWP, cardiac output (CO), diastolic pressure gradient (DPG), and PVR, assessed in stable clinical conditions. (12)

Table 2: Haemodynamic profile of pulmonary hypertension. (10)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Mean pulmonary artery pressure</th>
<th>Pulmonary capillary wedge pressure</th>
<th>Pulmonary vascular resistance</th>
<th>Clinacal groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated pre-capillary PH</td>
<td>&gt;20 mmHg</td>
<td>≤15 mmHg</td>
<td>≥ 3 WU</td>
<td>1, 3, 4 and 5</td>
</tr>
<tr>
<td>Combined pre- and post-capillary PH</td>
<td>&gt;20 mmHg</td>
<td>&gt;15 mmHg</td>
<td>≥ 3 WU</td>
<td>2 and 5</td>
</tr>
<tr>
<td>Isolated post-capillary PH</td>
<td>&gt;20 mmHg</td>
<td>&gt;15 mmHg</td>
<td>&lt; 3 WU</td>
<td>2 and 5</td>
</tr>
</tbody>
</table>

The 6th World Symposium on Pulmonary Hypertension defined three haemodynamic profiles of PH: Isolated pre-capillary PH, combined pre- and post-capillary PH, and isolated post-capillary PH. WU, Wood units.
Prognostic evaluation and risk assessment

A clinical assessment of patients with PH remains the most valuable tool to determine disease severity, improvement, stability or deterioration. There is no single variable that provides sufficient diagnostic and prognostic information; hence a comprehensive assessment is required.\(^{(12)}\) A multidimensional approach is needed to address the four questions that should be asked at each visit; any evidence of clinical deterioration?; if so, is clinical deterioration caused by progression of PH or by a concomitant illness?; is RV function sufficient and stable?; and is the current status compatible with a good long-term prognosis, i.e. does the patient meet the low-risk criteria (Table 3)?\(^{(12)}\)

High risk (>10% 1-year mortality) is defined as clinical signs of right heart failure, rapid progression, repeated syncope, World Health Organization functional class (WHO FC) IV, 6-minute walk (6MW) <165 m, B-type natriuretic peptide (BNP) 300 ng/L, pericardial effusion, right arterial pressure >14 mm Hg, cardiac index (CI) <2.0 L/m/m\(^2\), and mixed venous oxygen saturation (SvO\(_2\)) <60%.\(^{(12)}\)

Low risk (<5% in 1-year mortality) is defined as no signs of right heart failure, no progression of symptoms, WHO FC I, II, 6MW >440 m, BNP <50 pg/L, no pericardial effusion, normal right atrial (RA) size, RA pressure <8 mm Hg, CI ≥2.5 L/min/m\(^2\), and SvO\(_2\) >65%.\(^{(12)}\)

**Table 3: Risk assessment in pulmonary arterial hypertension.**\(^{(12)}\)

<table>
<thead>
<tr>
<th>Determinants of prognosis* (estimated 1-year mortality)</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5–10%</th>
<th>High risk &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope(^2)</td>
<td>Repeated syncope(^2)</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MW (m)</td>
<td>&gt;440</td>
<td>165–440</td>
<td>&lt;165</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak V(_\text{O}<em>2) &gt;15 m/min/m(^2) (≥65% pred.) VE/V(</em>\text{O}_2) slope &lt;3</td>
<td>Peak V(_\text{O}<em>2) 11–15 m/min/m(^2) (35–65% pred.) VE/V(</em>\text{O}_2) slope 36–44.9</td>
<td>Peak V(_\text{O}<em>2) &lt;11 m/min/m(^2) (&lt;35% pred.) VE/V(</em>\text{O}_2) slope ≥45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/L NT-proBNP &lt;300 ng/L</td>
<td>BNP 50–300 ng/L NT-proBNP 300–1400 ng/L</td>
<td>BNP &gt;300 ng/L NT-proBNP &gt;1400 ng/L</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &gt;18 cm(^2) No pericardial effusion</td>
<td>RA area 18–26 cm(^2) No or minimal pericardial effusion</td>
<td>RA area &gt;25 cm(^2) Pericardial effusion</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt;8 mmHg CI &gt;2.5 L/min/m(^2) SvO(_2) &gt;65%</td>
<td>RAP 8–14 mmHg CI 2.0–2.4 L/min/m(^2) SvO(_2) 65–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 L/min/m(^2) SvO(_2) &lt;65%</td>
</tr>
</tbody>
</table>

*Most of the proposed variables and cutoff values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for PAH and the cutoff values used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

\(^*\)Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

\(^*\)Repeate...
Pregnancy and Labour Physiology

Many physiological changes occur to the mother during pregnancy to meet the increasing demands of the growing foetus and some of these changes may contribute to right ventricular failure in women with PAH (figure 1). The changes most relevant to PH include those of the cardiovascular, respiratory and haematological systems. Blood volume, red cell mass, left ventricular mass and cardiac output (CO) increase during normal pregnancy, whereas systemic vascular resistance (SVR) and pulmonary vascular resistance decrease.\(^{(2, 4)}\)

The blood volume increases by 40-100% above pre-pregnancy baseline at its peak between 20-32 weeks of gestation.\(^{(4)}\) Red cell mass only increases to 25% compared to plasma which increases by 50-70% above pre-pregnancy level, potentially resulting in physiological anaemia.\(^{(6)}\) The heart size can increase by up to 30% partly due to dilatation and eccentric hypertrophy as a results of increased plasma volume. CO increases sharply in the first trimester and then gradually increases to peak values of around 30-50% above the pre-pregnancy baseline (figure 2).\(^{(3, 6)}\) The stroke volume increase of 35% contributes initially, whereas heart rate increase by 15-20 beats per minute contribute late in pregnancy.\(^{(6)}\)

\(\text{SVR} \rightarrow 10\%\)  
\(\text{Progesterone NO/prostacyclins} \)  
\(\text{↑ CO 30-50\% Stroke volume} \)  
\(\text{Heart rate} \)  
\(\text{↑ Coagulability} \)  
\(\text{↑ O}_2\) consumption  
\(\text{↑ Blood volume 40-100\%} \)  
\(\text{↑ Red blood cell mass 25\%} \)

\(\text{↑ Right-to-left shunt (PAH-CHD)} \)  
\(\text{Pulmonary embolism} \)  
\(\text{RV dilation RV failure} \)  
\(\text{Physiological anaemia} \)

\(\text{Hypoxia} \)  
\(\text{Hypotension} \)  
\(\text{LV underfilling ↓ CO} \)  
\(\text{↑ PVR} \)  
\(\text{Shock Respiratory failure} \)  
\(\text{Blood volume Vasoconal reflex} \)  
\(\text{↑ Venous return} \)  
\(\text{Delivery} \)

\textbf{Figure 1}: Physiological changes in pulmonary arterial hypertension (PAH) patients which occur in response to pregnancy. NO: nitric oxide; CO: cardiac output; PAH-CHD: PAH associated with congenital heart disease; LV: left ventricle; RV: right ventricle; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance.\(^{(6)}\)
The immense problem in the pregnant PH patient is that the physiological compensatory vasodilatory response of the pulmonary vasculature is decreased or absent, resulting to a significant increase in mPAP and PVR.\(^3\) The inability of pulmonary vascular bed to accommodate the increased CO results in significant RV afterload stress, strain and failure, as evidenced by deterioration most frequently between 20-24 weeks, during labor and delivery, or in the postpartum period.\(^3\) Deterioration in second trimester reflects an inability of the cardiopulmonary system to accommodate the increased CO and failure to meet the cardiovascular demand, while deterioration during labor and delivery or in postpartum period is frequently triggered by volume shifts and intravascular pressure swings, as well as the negative effects of pain, Valsalva maneuvers, hypoxia, and acidosis on the pulmonary vascular tone and or RV function.\(^3\)

Pregnancy is a hypercoagulable state owing to increased platelet aggregation, increased concentration of fibrinogen, the development of progressive resistance to protein C and decrease in protein S levels and as well as impaired venous return by the enlarged uterus. These changes increases the parturients risk of both pulmonary and peripheral vascular thrombosis.\(^2,8\)

![Figure 2: Changes in cardiac output (CO), mean arterial pressure (MAP), and systemic vascular resistance (SVR) during pregnancy. Values above dotted line represent an increase from baseline, while values below dotted line depicts a decrease.](image)

**Maternal and Fetal Outcomes**

PAH in nonpregnant patients has been associated with poor outcomes, with a reported 50% survival rate of 2.8 years in the era before availability of PAH-specific treatments, and with targeted-treatment an average survival rates of 50% at 7 years.\(^3\) It is therefore not surprising to witness a poorer outcome in PAH patients who become pregnant.
Two previous systematic reviews described the outcome of pregnant women with PH in different treatment eras. The first review by Weiss et al. covered the years 1978-1996 and described 125 pregnancies. Maternal mortality was observed in 38% of these pregnancies and 30% in idiopathic PAH (IPAH, formerly called “primary PH”), 36% in Eisenmenger syndrome, and 56% in associated PAH.\(^3\)\(^8\) The second review (Bédard et al.), covered the years 1997-2007, and included 73 pregnancies. Maternal mortality was 25%, which was significantly lower than in previous era (P=0.047). Women with IPAH had a mortality of 17%, mortality in women with PH related to congenital heart disease (CHD) was 28%, and in women with other causes of PH, it was 33%.\(^8\) Most deaths (78%) occurred after delivery in both reviews.\(^8\) Independent predictors of maternal mortality were late diagnosis and late hospital admission in the early era. Bédard et al. found parturient's who received general anaesthesia were 4 times more likely to die than those receiving regional anaesthesia.\(^3\) Importantly, PAP and New York Heart Association (NYHA) functional class were not predictors of outcome in both reviews.\(^8\)

Pieper et al (1998-2013) reviewed 31 studies with 77 parturient's managed with targeted pulmonary hypertension treatments (table 4). Mortality occurred in 12 women (16%). Three women (9%) died in the IPAH group (n=32), in CHD-PAH (n=30) seven women (23%) died, and mortality in the other PH group (n= 15) was 13%. The targeted pulmonary hypertension therapies were used by 39% of the women. Majority received anticoagulation therapy (83%). Out of the thirteen women who received targeted pulmonary hypertensive therapy during delivery, postpartum or both, six died (46%), compared with 9% in the group of women in which targeted therapy was started at least a week before their deliveries (P=0.017).\(^8\)

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<tbody>
<tr>
<td>Total mortality</td>
<td>48/125 (38%)</td>
<td>18/73 (25%)</td>
<td>12/77 (16%)</td>
</tr>
<tr>
<td>Mortality, IPAH</td>
<td>8/27 (30%)</td>
<td>5/29 (17%)</td>
<td>3/32 (9%)</td>
</tr>
<tr>
<td>Mortality, CHD-PAH</td>
<td>26/73 (36%)</td>
<td>8/29 (28%)</td>
<td>7/30 (23%)</td>
</tr>
<tr>
<td>Mortality, oPH</td>
<td>14/25 (56%)</td>
<td>5/15 (33%)</td>
<td>2/15 (13%)</td>
</tr>
</tbody>
</table>

CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; IPAH, idiopathic pulmonary arterial hypertension; oPH, other cause of pulmonary hypertension.

**Multidisciplinary Team Approach**

The multidisciplinary team looking after PH pregnant patients should be formed by PH specialist, a cardiologist, an obstetrician, an anesthetist specialised in managing high risk pregnancies, neonatologist, pharmacist, intensivist and social workers should be consulted early.\(^3\) The implications of discovering the BMPR2 mutation as the most common genetic cause of PAH, accounting for 80% of HPAH and 20% of IPAH meant genetic counseling for the at risk parturient should be done by a specialist trained in genetics.\(^10\)
Figure 3. Recommended evaluation of and follow-up for a pregnant patient with pulmonary arterial hypertension (PAH). BNP: brain natriuretic peptide; endothelin receptor antagonist; FC: World Health Organization functional class; ICU: intensive care unit; LMWH: low-molecular-weight heparin; PH: pulmonary hypertension; RV: right ventricular; 6MWT: 6-minute walk test. (9)

**Pharmacological management**

The treatment approach is guided by the diagnosis of the PH type (WHO clinical classification, Table1) patient’s haemodynamic status and disease severity. (9) The overall risk of thromboembolic events is 5-fold higher in pregnant than in nonpregnant state. (1) Anticoagulation is usually prescribed in patients in group 1 (idiopathic PAH and inheritable PAH) and group 4 (chronic thrombo-embolic PH) patients are on lifelong therapy. (8) With the risk of bleeding in women with portal hypertension or Eisenmenger’s syndrome, the use of anticoagulation is therefore controversial.

Vitamin K antagonists are associated with dose dependent teratogenesis when used in the first trimester and additional risk of foetal intracranial bleeding throughout pregnancy. (8) Low molecular weight and unfractionated heparin do not cross the placenta, making them safe for use during pregnancy. (3) The role of direct oral anticoagulants (DOAC) in pregnancy still needs further research, therefore they are classified as category C drugs. (3)

When clinical signs of cardiac failure are present, diuretics (furosemide, hydrochlorothiazide) digoxin and sodium/fluid restriction are recommended. (13) Spironolactone should be avoided due to its association with anti-androgenic effects in male animal foetuses. (12)

PH is a rare disease, and trials with large number of patients and long-term follow up are difficult and expensive to perform, especially when survival is the primary outcome. (11) The concept of “hit hard and hit early” has been suggested, advocating for dual or triple therapy early in an attempt to halt disease progression. (11) RHC is mandatory before initiation of drug therapy, unfortunately in a recent review, up to 40% of referred patients were already on drug therapy without having done RHC.
Treatments specific for PH include: Calcium channel blockers, prostaglandin analogues, phosphodiesterase inhibitors, inhaled nitric oxide, Guanylate cyclase stimulators, and endothelin receptor antagonist. Despite different mechanisms of action, all of them eventually lead to pulmonary vasodilation, as shown in figure 4. Individual description of these drugs follows and table 5 shows risk category of these drugs in pregnancy.

**Figure 4**: Target therapies for pulmonary hypertension. All classes of drugs belong to one of the pathways described, and the end results is decreased pulmonary vascular resistance. Antagonists are highlighted in red while agonist are in green. ECE, endothelin converting enzyme; ET-A, endothelin receptor A; ET-B, endothelin receptor B; PLC, phospholipase C; IP3, inositol triphosphate; NO, nitric oxide; PDE 5, phosphodiesterase 5; sGC, soluble guanylate cyclase; AC, adenylate cyclase.

(Calcium channel blockers (CCB))
Nifedipine, diltiazem, or amlodipine are the mainstays. Mainly reserved for group 1 (PAH) who are vasodilatory responders on RHC. They are contra-indicated in non-responders (90% of patients). Low cost and widespread availability make them attractive as initial agents. Non-selective pulmonary vasodilators result in systemic side effects, therefore they are not suitable for high-risk patients (WHO class III/IV).

(Prostaglandin analogues)
Prostacyclin’s are the most studied agents and have a proven survival benefit. They produce vasodilatation through a second messenger system, leading to increased cAMP levels (figure 4).

I. Epoprostanol: it has a very short half-life (<6 min) therefore must be infused continuously via a central line. Significant risk of rebound worsening with abrupt/inadvertent interruption of the infusion within 30 minutes.

II. Treprostinil: 3-hour half-life, IV or SC routes of administration. Equivalent efficacy to epoprostanol and stable in room temperature. Major problem of pain and erythema at the infusion site.
III. Iloprost: Inhalational route of administration is its main advantage. Treatment effects for only 30-90 minutes of administration, thus 6-9 nebulizer treatments per day are required (5-15 minutes per treatment). Overall benefits are questionable.

**Phosphodiesterase inhibitors**
Sildenafil and tadalafil inhibit the phosphodiesterase (PDE)-5 enzyme, causing cGMP levels to build up, leading to increased intracellular NO signaling and vasodilation.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) Being relatively low cost (compared with other PH drugs) is advantageous, but this is offset by development of tolerance requiring frequent dose adjustments.\(^1\)\(^)\ Sildenafil has shown improvement in 6 minute walk test as well as meliorate the rebound increase PVR and PAP after discontinuation of NO.\(^1\)\(^)\)

**Inhaled nitric oxide**
Selective pulmonary vasodilator requiring a dedicated delivery device to administer iNO into ventilator circuit, and this is not readily available. Risk of accumulation of toxic metabolites, necessitating continuous monitoring. It can cause rebound pulmonary hypertension after prolong exposure, thus slow weaning and bridging with oral medication is strongly advised.\(^1\)\(^)\)

**Guanylate cyclase stimulators**
Riociguat stimulates the soluble enzyme guanylate cyclase, which increases cGMP production inside the cell.\(^1\)\(^)\) It has been approved by FDA for use in inoperable patients with CTEPH and PAH. Oral route of administration, with hypotension as the side effect in 9% of patients. It improves 6MWD test, functional class, haemodynamic parameters and the B-type natriuretic peptide (BNP) preform, NT-proBNP.\(^1\)\(^)\)

**Endothelin receptor antagonist**
Endothelin (ET) is a potent vasoconstrictor and a smooth muscle mitogen that may contribute to the increase in vascular tone and pulmonary vascular hypertrophy associated with PAH.\(^1\)\(^,\)\(^3\) Bosentan, ambrisentan, and macitentan all given orally, block the ET receptors. Improvement in haemodynamics and functional capacity have been demonstrated. Side effects including hepatotoxicity, thrombocytopenia, anaemia, teratogenicity have been reported. Category X in pregnancy.\(^1\)\(^,\)\(^3\)\)
**Table 5.** US Food and Drug Administration assigned risk category for pulmonary hypertension drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy risk categorya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td>B</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>B</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>B</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>B</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>C</td>
</tr>
<tr>
<td>Iloprost</td>
<td>C</td>
</tr>
<tr>
<td>Bosentan</td>
<td>X</td>
</tr>
<tr>
<td>Ambrisantan</td>
<td>X</td>
</tr>
<tr>
<td>Macitentan</td>
<td>X</td>
</tr>
<tr>
<td>Riociguat</td>
<td>X</td>
</tr>
</tbody>
</table>

Note: FDA: US Food and Drug Administration; PAH: pulmonary arterial hypertension.

a B: animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate, well-controlled studies in pregnant women; C: animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate, well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; X: studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse-reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

**Termination of pregnancy**

There are a number of circumstances that pregnant patients with PH may present to the health care professionals. Due to the high risk to mother and foetus associated with pregnancy and PH, termination should be offered regardless of WHO functional classification or other markers of prognosis. Therapeutic termination of pregnancy is usually performed in first trimester. It should be considered in the second trimester up to point of foetal maturity guided by religious, cultural preferences and legal framework in different countries.

**Timing and mode of delivery**

The timing of admission and delivery is determined by the clinical status of the mother and foetal growth. In those with severe disease a prolonged in-hospital admission and early elective delivery (often from 34 weeks) is preferable, always balancing the risk of foetal prematurity and maternal risk.

The mode of delivery should be carefully selected in the pregnant PH patient as it will influence the outcome. Vaginal delivery is usually associated with less bleeding, decreased risk of infection and lower thromboembolic risk, but should be avoided in patients with PAH as it carries a multitude of physiological disadvantages:

1. Valsalva maneuver (decreased venous return [VR] resulting in reduction of preload dependent CO, precipitating cardiopulmonary collapse).
2. Vasovagal response (decreased VR, reduce preload and result in cardiopulmonary collapse).
3. Pain of childbirth (sympathetic nervous system stimulation resulting in increased HR and systemic and pulmonary vascular tone, leading to haemodynamic instability.

4. Uterine contraction (autotransfusion of approximately 500ml of blood and increase of VR due to relief of inferior vena cava obstruction combined increase preload and precipitate right heart failure).

5. Labor induction (agents used to induce labor, like prostaglandin E, produce pulmonary vasodilatation, whereas prostaglandin F2α induce pulmonary vasoconstriction and oxytocin are to be used with caution as it can drop SVR and also increase PVR).\(^{(2, 3)}\)

Cesarean section (C/S) is the preferred mode of delivery and should be used unless not available or in case of emergencies.\(^{(2, 3, 15)}\) Cesarean section bypasses the complications associated with labour as mentioned above. However, the choice of anesthesia for C/S is important and most units would consider regional anaesthesia in preference to general anaesthesia.\(^{(3)}\) The choice of anaesthesia will be discussed later on.

**Labor analgesia**

Early and effective analgesia is critical to maintain SVR and PVR balance to avoid catecholamine surges from pain.\(^{(13)}\) The ideal is a combined spinal epidural (CSE) in the first stage of labor with intrathecal opioid, as long as the placement is not contraindicated by anticoagulation. Alternatively a low dose remifentanil infusion or patient controlled analgesia are suitable.\(^{(13)}\)

**Preoperative Evaluation**

PH affects multiple organ systems simultaneously (lung, heart, and vascular system), therefore preparation for surgical procedure should be considered as the joint task of anaesthesia, surgery, pulmonology and cardiology.\(^{(9)}\) The goal of the pre-op evaluation is to firstly determine if the patient suffers from PH, RV failure, or a combination of these, and secondly to optimise the patients initial condition as far as possible by adjusting the current specific medication and treatment of comorbidities. This approach reduces the individual risk of complications.\(^{(8, 13)}\) The Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL 2.0) risk calculator can help both clinicians and patients in making informed treatment decision.\(^{(10)}\)

**History and Physical Examination**

Symptoms of pulmonary hypertension are non-specific and may include chest pain, cough, and shortness of breath induced initially by exertion.\(^{(13)}\) Symptoms at rest occur in advanced cases. The development of right heart failure results in lower extremity swelling, dizziness, or syncope. Some patients may present with mechanical complications of PH and abnormal distribution of blood flow in the pulmonary vascular bed. These include hemoptysis related to rupture of hypertrophied bronchial arteries, as well as symptoms attributable to pulmonary arterial dilatation such as hoarseness caused by compression of the left recurrent laryngeal nerve, wheeze caused by large airway compression and angina due to myocardial ischemia caused by compression of the left main coronary artery.\(^{(12, 15)}\) The majority of these symptoms overlap with that of normal pregnancy.
Figure 5: Diagnostic approach to pulmonary artery hypertension (from the ACC/AHA 2009 Expert Consensus Document on Pulmonary Hypertension). 6MWT: 6-minute walk test; ABG: arterial blood gases; ANA: antinuclear antibody serology; CHD: congenital heart disease; CPET: cardiopulmonary exercise test; CT: computerized tomography; CTD: connective tissue disease; CXR: chest x-ray; ECG: electrocardiogram; echo: echocardiogram; HIV: human immunodeficiency virus screening; HTN: hypertension; LFT: liver function test; PE: pulmonary embolism; PFT: pulmonary function test; PH: pulmonary hypertension; RA: rheumatoid arthritis; RAE: right atrial enlargement; RH Cath: right heart catheterization; RVE: right ventricular enlargement; RVSP: right ventricular systolic pressure; SLE: systemic lupus erythematosus; TEE/TOE: transoesophageal echocardiography; VHD: valvular heart disease; VQ scan: ventilation-perfusion scintigram.

Table 5: Functional Classification of Pulmonary hypertension (WHO 1998)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>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.</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest.</td>
</tr>
</tbody>
</table>
Physical signs of PH include left parasternal lift, an accentuated pulmonary component of the second heart sound (P2), a RV third heart sound (S3), a pansystolic murmur of tricuspid regurgitation and a diastolic murmur of pulmonary regurgitation. Elevated jugular venous pressure, hepatomegaly, ascites, peripheral edema and cool extremities in advanced disease.\textsuperscript{12,15} Clinical examination may suggest an underlying cause of PH and together with the investigations as summarized in figure 5 above will complete the assessment of this challenging disease.

**Investigations**

**Blood Test**
A full blood count, metabolic panel, coagulation studies and a preoperative arterial blood gas should be done. Biomarkers such as brain natriuretic peptide (BNP) are useful in monitoring chronic PAH. In pulmonary embolism, BNP can stratify patients at risk of RVF and troponin I leak may predict mortality.\textsuperscript{4}

**Electrocardiogram**
Electrocardiogram (ECG) may provide supportive evidence of PH, but a normal ECG does not exclude the diagnosis. The ECG abnormalities may include P pulmonale, right axis deviation, RV hypertrophy, RV strain, right bundle branch block, and QTc prolongation. Presence of prolonged QRS complex and QTc suggest severe disease. Supraventricular arrhythmias particularly atrial flutter, but also atrial fibrillation may occur in advanced disease.\textsuperscript{12}

**Chest radiograph**
In IPAH the chest radiograph is abnormal in 90\% of patients at the time of diagnosis. The findings in patients with PAH include pulmonary arterial dilatation, which contrast with ‘pruning’ (loss) of the peripheral blood vessels. Right atrium (RA) and RV enlargement in more advanced cases. The chest radiograph may assist in differential diagnosis of PH by showing signs suggesting lung disease (group 3) or pulmonary venous congestion due to left heart disease (group 2).\textsuperscript{12}

**Special investigations**
The gold standard for the diagnosis of PH is right heart or pulmonary artery catheterization. In the resource constrained environment this is not necessarily done. RHC directly measures the mean PAP and yields other useful haemodynamic data. For example, it measures cardiac output and calculates PVR according to Ohm’s law. A low CO is a marker of poor prognosis.\textsuperscript{11}

Ventilation/perfusion (V/Q) lung scan can be used in patients with PH to look for chronic thromboembolic PH.\textsuperscript{12} CT imaging (high-resolution, contrast-enhanced and pulmonary angiography) are all available to help provide important information on vascular, cardiac, parenchymal and mediastinal abnormalities to find the cause of PH.\textsuperscript{12} Cardiac magnetic resonance (CMR) imaging may be useful in patients when ionizing radiation exposure or iodine-based contrast media injection is contraindicated.\textsuperscript{12}
What is most accessible is the transthoracic echocardiograph (TTE), it is used to image the effects of PH on the heart and estimate PAP from continuous wave Doppler measurements non-invasively.\(^{(12)}\) The estimation of systolic PAP is based on the peak tricuspid regurgitation velocity (TRV) taking into account right atrial pressure (RAP) as described by the simplified Bernoulli equation \(\triangle P=4V^2\). The systolic PAP is equivalent to right ventricular systolic pressure (RVSP) in the absence of right ventricular out-flow tract obstruction (RVOT) or pulmonary stenosis. The mean PAP can be approximated with the equation \(\text{mPAP} = [0.61 \times \text{sPAP}] + 2\), therefore a sPAP of 40mmHg usually implies a mPAP of more than 25mmHg implying presence of pulmonary hypertension.\(^{(11, 12)}\) Figure 6 and Table 6 demonstrate the usefulness of echocardiography as the screening tool in patients with suspected pulmonary hypertension using TRV and the ventricles, pulmonary artery, right atrium and inferior vena cava.
The measure of function in PH can be done using the following parameters: myocardial performance index of RV (Tei index), systolic wave velocity, isovolumic relaxation time (IVRT) and tricuspid annular plane systolic excursion (TAPSE). These measurements can be used as prognostic indicators for example, a TAPSE of less than 15mm is associated with significant high risk of mortality.
The echocardiography report where PH is suspected should emphasise on PAP, right heart chamber size and function and any finding that may indicate a secondary cause. If PH is confirmed than the report should also include the various prognostic parameters (right atrial volume index, inferior vena cava diameter, eccentricity index, presence of pericardial effusion and TAPSE). Finally, it is important for the reporter of the echocardiography result not to judge severity of PAH on the basis of estimated sPAP, instead conclude on the severity of RV impairment. For a more comprehensive information on echocardiography for patients with PH, a reader is encourage to go through references 15 and 16 as this is an extensive topic on its own.

### Intraoperative Management

**Anaesthetic and haemodynamic goal**

1. Avoid elevations in PVR: Prevent hypoxaemia, acidosis, hypercarbia and pain.
2. Maintain SVR: Decreasing SVR dramatically reduces CO due to “fixed” PVR.
4. Avoid myocardial depressants and maintain myocardial contractility.
5. Maintain sinus rhythm.
Target for haemodynamic goals in the perioperative period include: mPAP within 15% of baseline; PASP less than 40mmHg of systolic arterial pressure; PVR <1/2 of SVR or close to baseline; CI >2.2 lmin⁻¹m⁻²; MAP ≥ 65 or 20mmHg above mPAP; RAP: the lowest value possible to allow systemic perfusion.\(^{(11)}\)

**Monitoring**

Basic monitoring
- ECG
- SaO\(_2\)
- End-expiratory CO\(_2\)
- Invasive blood pressure
- Optional: stroke volume variation (SVV)

Extended monitoring
- Pulmonary arterial catheter (PAC)
- Transoesophageal echocardiography (TOE)

Intraoperative use of PAC is still subject to controversial discussion in the current literature and most evidence is from case reports.\(^{(9, 13)}\) TOE may provide the best real time monitor of cardiac preload and of the status of right-to-left shunting, but requires general anaesthesia.\(^{(13)}\)

**Choice of Anaesthesia**

The selection of the anaesthetic team is just as crucial as selection of the anaesthetic technique to be used. With senior, experienced anaesthesiologist being present as the ideal.\(^{(9)}\) Historically, regional anesthesia was thought to be contraindicated and general anaesthesia was the standard. A recent review of cases of non-cardiac surgery including labor analgesia and cesarean section in Eisenmenger’s syndrome showed that regional anaesthesia is indeed safe for these patients.\(^{(13)}\)

**General anaesthesia**

General anesthesia (GA) is well known to depress cardiac contractility, increase PAP (laryngoscopy and intubation), and increase PVR (positive-pressure ventilation).\(^{(2, 3, 13)}\) Controversies of using GA in patients with PH still exist. Studies by Bédard and others suggested that pregnant patients with PH who received GA, were more likely to die than parturients receiving regional anaesthesia. However, these results should be viewed with caution as selection bias may be shown towards the sicker patient receiving general anaesthesia.\(^{(3)}\)

**Conduct of GA:**\(^{(13)}\)
1. Sedation: supplemental oxygen and avoid sedation preoperative to minimise hypoxia and hypercarbia risk.
2. Induction: Slow titration of induction agents is preferred avoiding haemodynamic instability associated with rapid sequence induction. Propofol and thiopental is to be used with extreme caution due to marked reduction in SVR. Ketamine and etomidate are considered appropriate. Blunting intubation response with short acting opioids and lignocaine is vitally important.
3. The risk of aspiration is increased with slow titrated induction in the pregnant state, thus strict NPO guidelines and pharmacological prophylaxis, with gentle bag-mask ventilation and cricoid pressure being recommended.

4. Maintenance of anaesthesia: careful titration of intravenous agents (midazolam or ketamine, Nondepolarizing NMB devoid of histamine release, and inhalational agents at concentrations of less than 0.5MAC.

5. Fluid management: Maintain euvo lemia as close to baseline as possible. Use CO monitoring that you are familiar with and has lowest risk to the patient to guide fluid management.

6. Haemodynamic Management: Assuming euvo lemia, inotropy therapy must be considered.
   a. Dobutamine (Beta₁ agonist) or Milrinone (PDE III inhibitor) as inotropic therapy. Both agents are “inodilators” and phenylephrine or noradrenaline can be used to treat the systemic vasodilatation.
   b. Inhaled nitric oxide (NO) is a pulmonary vasodilator, that requires special equipment for in line administration in the ventilatory circuit, and not every hospital have NO available. Inhaled prostacyclin can also be used intraoperatively either continuous or hourly inhaled bolus.

7. Ventilator management: Avoid hypoxia, hypercarbia and lung hyperinflation. Employ low tidal volume ventilation with low PEEP levels while also ensuring adequate respiratory rate to prevent hypercarbia.

**Regional anaesthesia**

Single shot spinal anaesthesia is contraindicated in the parturient with PH, due to the risk of a rapid rise in block height which may cause uncontrollable haemodynamic instability.² ³ ¹² Epidural anaesthesia with incremental dose has traditionally been considered the best approach to regional anaesthesia.² However, the low-dose combined spinal epidural anaesthesia (CSE) has gained popularity with the advantage of a better denser perineal sensory block when compared to epidural alone, with little additional risk of hypotension.² ³

**Postoperative Management**

The immediate postoperative period and up to 4 weeks after delivery represent a high risk period for sudden death in patients with PH.⁶ ¹³ The major contributors to this high mortality being right ventricular failure due to autotransfusion, excessive increase in PVR and thromboembolic events.⁶ Hence, PH patients should be closely monitored in intensive care units and the period of monitoring determined by their clinical course.⁹ Good analgesia (epidural), PH targeted therapy( iNO, prostacyclin’s), vasopressors, inotropes, anticoagulants (LMWH) and uterotonics (oxytocin) for prevention of bleeding, all should be used meticulously with the same multidisciplinary team approach.² ⁶ Breastfeeding is usually not recommended for patients on pulmonary vasodilators as they are excreted in breast milk and a negative prolactin effect on the myocardium cannot be excluded.⁶
Special Circumstances

Cardiopulmonary resuscitation (CPR) in PAH. Hoeper et al described the experience of physicians across 17 centers in the USA and in Europe between 1997 and 2002; of 3120 patients with PH treated in these centers, 513 (16%) had cardiac and respiratory arrest. CPR was attempted in 132 patients and was unsuccessful in 79% of these. Only 8 patients (6%) survived at 90 days without neurological deficits. Of those that survived the initial CPR, almost all had a reversible cause. The management option of patients with decompensated PAH not on an active transplant list are limited. Those already on the transplant list, extracorporeal life support may be a realistic bridge to transplant. It may be reasonable, for the patient with advanced PAH, to have an advanced care plan, including a ‘do not attempt resuscitation’ (DNAR) order.

ECMO (veno-arterial extracorporeal membrane oxygenation) should be considered for selected patients with PH and RV failure. A veno-venous approach may improve oxygenation, but not the unloading of the RV as a result not suitable for this PH patients. ECMO can be used either as bridge to recovery or bridge to transplantation.
CONCLUSION

Pregnancy in PAH is a highly delicate topic. Improved management has shown a decrease in mortality in all subgroups of pregnant women with Pulmonary Hypertension. However, despite this mortality remains significantly high especially during labor and the immediate postpartum period necessitating close monitoring in an intensive care unit.\(^6\)

Hence, the current guidelines recommend women with PH not to fall pregnant and if they do, termination of the pregnancy should be offered no matter the severity of the disease.\(^3, 12\) A multidisciplinary approach at a tertiary facility, with early targeted pulmonary hypertension therapy and early delivery have contributed to favorable outcomes in recent reviews.

The safest anaesthetic technique in these patients is still controversial due to the lack of randomised control trials to evaluate outcomes. However, deemed inappropriate in the past, regional anaesthesia in these patients is gaining popularity and has shown favourable outcomes. As with all patients, the anaesthetic should be tailored to each patient, according to the severity of disease and planned mode of delivery.
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12. Authors/Task Force Members: Nazzareno Galie* (ESC Chairperson) (Italy), Marc Humbert*a (ERS Chairperson) (France) J-LVB, Simon Gibbs (UK) ILA, Adam Torbicki (Poland), Ge rald Simonneau (France), Andrew Peacocka (UK), Anton Vonk Noordegraaf (The Netherlands), Maurice Beghettib (Switzerland), Ardeschir Ghofrania (Germany), Miguel Angel Gomez Sanchez (Spain) GHG, Walter Klepetkoc (Australia), Patrizio Lancellottii (Belgium), Marco Mutuccid (Italy), Theresa McDonaghi (UK), Luc A. Pierard (Belgium), Pedro T. Trindade (Switzerland), Maurizio Zompatorie (Italy) and Marius Hoepera (Germany). 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
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