Β5.Γ. PULMONARY HYPERTENSION IN PREGNANCY

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Pulmonary hypertension is defined by a mean pulmonary arterial pressure of at least 25mmHg at rest as assessed by right heart catheterization. Based on the left-sided filling pressure the haemodynamic definition further distinguishes pre- (≤15 mmHg) and post-capillary (>15 mmHg) PH. The clinical classification of PH is categorized into five groups of multiple etiology according to clinical presentation, pathological findings, haemodynamic characteristics and treatment strategy(Table1).

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

Table 1. Haemodynamicand clinical definitions of pulmonary hypertension (*From Ref.10 with permission*)
Abbr. CO=cardiac output; DPG=diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP=mean pulmonary arterial pressure; PAWP=pulmonary arterial wedge pressure; PH=pulmonary hypertension; PVR=pulmonary vascular resistance; WU=Wood units. [a]All values measured at rest; [c]Wood Units are preferred to dynes.s.cm^{-5}.

PH and particularly pulmonary arterial hypertension (PAH) are highly morbid conditions.PAH is an enigmatic vascular disorder characterized by pulmonary vascular remodeling and increased pulmonary vascular resistance, ultimately resulting in pressure overload, dysfunction, failure of the right ventricle and death. Groups 4 and 5 may be as severe as PAH, while Groups 2 and 3 are characterized by less severe remodeling.

Current medications for PH improve pulmonary vasomotor tone but do not reverse or prevent disease progression, thus 3-year mortality remains high at 55%. Current diagnostic strategies are also suboptimal for detecting early-stage disease. The origin of PH is shifted towards a metabolic theory, the basis of which is founded in molecular and cellular processes asobserved in cancer that leads to hyperproliferation, inflammation and resistance to apoptosis. Increasing evidence in PAH reveals aberration of metabolism not only in the pulmonary vasculature but also within the right ventricle and skeletal muscles suggesting systemic effects in disease pathogenesis. Emerging metabolic therapies are promising in overcoming the barriers in treatment.

PAH is frequently encountered in females and the first clinical manifestations may be seen in pregnancy. Mortality remains high in pregnancy 16–30%; there is also

increased fetal and neonatal mortality 0–30%, particularly if there is preterm delivery, reduced maternal cardiac output and/or hypoxaemia.

ESC2018 guidelines for the management of cardiovascular diseases during pregnancy recommend the avoidance of pregnancy in women with PAH (**IIIC**) and termination discussed when pregnancy does occur. The greatest risk is in the peripartum and the post-partum period. Pulmonary hypertensive crisis, pulmonary thrombosis and right heart failure are the most common causes of death and may occur even in patients with few symptoms prior to pregnancy.

Fatigue and dyspnoea are the most frequent presenting symptoms in PH. Since these symptoms also occur in healthy pregnant women, the diagnosis during pregnancy may be delayed. Echocardiography will usually reveal the diagnosis and the threshold to ask for it should be low during pregnancy in women with dyspnoea. Chest pain is often present and reflects right ventricular ischemia. Syncope can result from low cardiac output. Several signs of right heart failure, such as hepatomegaly, ascites, and ankle oedema, may be hard to identify during pregnancy or resemble to normal pregnancy signs.

The usual diagnostic algorithm of PH should be followed when a pregnant patient presents with newly diagnosed PH. Right heart catheterization is recommended to confirm the diagnosis of PAH under very strict indications(**IC)**,such as diagnostic uncertainty and to assist important therapeutic decisions. If this is required, it should be performed in a specialist centre.

Immediate initiation of therapy and periodic follow-up (often weekly in the third trimester) by a pregnancy heart team, involving obstetric and cardiac anesthesiologists, high-risk experienced obstetricians, neonatologists, cardiologists and specialists in the treatment of pulmonary hypertension, is mandatory for women who wish to continue with their pregnancy. Genetic counselling is appropriate in familial cases. A full assessment, including oxygen saturation and assessment of right ventricular function, should occur at each visit. Bed rest may be required in symptomatic patients and additional risk factors (such as air travel) avoided. A detailed delivery plan, including the optimal mode and timing of delivery, should be decided. This should include the post-partum need for intensive care and mechanical support.

Treatment during pregnancy depends on WHO functional status and right ventricular function. If a PAH patient conceives on targeted PH therapies, consideration should be given on withdrawing embryotoxic drugs taking account the risks of withdrawal (**IIa**). The subset of patients with true vasodilator responsiveness who are well controlled on calcium channel blocker therapy may be at lower risk and this therapy should be continued, as should all i.v. therapies. Thrombo-embolism is a major risk and anticoagulation is recommended in pregnant patients with chronic thromboembolic pulmonary hypertension (**IC**). Diuretics may be needed in patients with heart failure and iron deficiency should be treated.

Risk stratification should be performed as in non-pregnant patients. All PAH pregnant women are categorized into modified WHO IV classification of cardiovascular risk with maternal cardiac events rate at 40-100%. Risk factors for maternal death are: severity of PAH, late hospitalization and perhaps the use of general anesthesia. Higher mortality is associated with severe right ventricular systolic pressure (RVSP) >70 mmHg, uncontrolled PH, poor mother's functional status and emergency surgery.

For all modes of delivery it is important that the underlying PH is well controlled first. In treatment-naive pregnant PAH patients, initiating treatment should be considered (**IIaC**).At some centers there is a preference for i.v. epoprostenol initiation immediately prior to delivery. Even if women have evidence of well compensated PH prior to delivery, acute deterioration and death can occur post-partum; therefore,

treatment with i.v. epoprostenol is continued at some centers for some time after delivery.

Elective caesarean section in 32^{nd}–36^{th} gestation week is recommended as preferred mode of delivery to avoid the hemodynamic side-effects and the unpredictable timing of a vaginal delivery. Regional anesthesia is favored over general anesthesia, as general anesthesia is associated with a four-fold increase in maternal mortality. Epidural with slow and incremental loading or low-dose combined spinal-epidural anesthesia are preferable.

Continuous hemodynamic monitoring of arterial and central venous pressure is advised prior to induction of anesthesia. The routine placement of a pulmonary artery catheter is no longer recommended. Noninvasive cardiac output monitors have become increasingly popular in the management of high risk patients. Echocardiography is an essential diagnostic tool to gather information and guide therapy.

Vagal reactions and syncope can have catastrophic consequences in PH patients, because the right ventricle is extremely preload dependent and compensatory mechanisms are limited. Pregnant PH patients and their providers should be counseled on inducers and symptoms of vasovagal syncope. Common inducers during pregnancy include vena cava compression, rapid positional changes (especially getting up too fast), pain, anxiety, straining while pushing during vaginal delivery, hypovolemia, anemia, hyperthermia, and hyperventilation. Iatrogenic causes include administration of vasodilators, interventions that induce vasodilation and decrease venous return (e.g., induction of general or spinal anesthesia), manipulation of the cervix, and any procedure that causes pain and/or anxiety. Common preceding symptoms of vasovagal syncope include nausea, diaphoresis, lightheadedness and pallor.

The goals of anesthetic management are maintenance of sinus rhythm, optimization of right ventricular (RV) preload, enhancement of RV contractility, avoidance of hypoxic pulmonary vasoconstriction and high airway pressures. Systemic vasoconstriction improves coronary perfusion pressure without fear from additional pulmonary vasoconstriction. Selective pulmonary vasodilators that can be used are:

- inhaled iloprost (5–10μg diluted in 10ml saline, nebulized over 10min, repeated every 2–4h)
- inhaled NO (5–40 ppm continuously)
- intravenous milrinone (at infusion of 0,25-0,75 μg/kg/min, initial 50 μg/kg bolus)

Uterotonic medication, routinely administered after delivery to decrease the risk of uterine atony and postpartum hemorrhage, should be given only with utmost caution, at the lowest effective dose and never as a bolus.

In the first 72h postpartum, the hemodynamic changes reach their peak and may lead to acute cardiac failure in patients with compromised RV function necessitating close monitoring and treatment in ICU. The highest risk of mortality is during the first 4weeks up to two months postpartum, therefore a close, long-term follow-up should be secured and therapies that reduce the risk of right ventricular failure should not be discontinued in the early post-delivery period. Breast feeding is not usually recommended, as pulmonary vasodilators may be excreted in breast milk and a negative effect of prolactin on the myocardium cannot be excluded in these patients. Individualized counselling is needed to discuss the need for ongoing therapies and the avoidance of future pregnancies.

In conclusion, pulmonary hypertension in pregnancy is difficult to deal with. Women with PH who become pregnant warrant a multidisciplinary team approach for the management of pregnancy, delivery and postpartum. Close and continuous communication between all specialties is mandatory to improve clinical outcome for both mother and neonate.

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