Pulmonary arterial hypertension in pregnant women (PAH). Update

Hipertensiunea arterială pulmonară la femeile gravide (HAP). Update

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Abstract

Pulmonary arterial hypertension (PAH) represents a substantial risk factor associated with high mortality in pregnant women, a reason why a pregnancy is a contraindication in patients who are diagnosed with this condition. Pathophysiological changes induced by pregnancy and childbirth have negative effects on the pulmonary vasculature and the right side of the heart. Young age of pregnant women, non-specific symptoms or asymptomatic forms, especially in early diagnosis of PAH, and lack of monitoring pregnancy may lead to confusion or misdiagnosis. In PAH patients, continuation of pregnancy involves establishing a specialist-run multi-disciplinary team for monitoring and assessing intrapartum delivery and postpartum management. Despite advances in PAH treatment, guidelines strongly discourage pregnancy in PAH patients. Successful outcome could be possible with experienced teams in a high-specialized Ob-Gyn delivery unit.
Keywords: *pulmonary arterial hypertension (PAH), pregnancy, delivery, PAH treatment, peri- and postnatal mortality*

Rezumat

Hipertensiunea arterială pulmonară (HAP) la femeile gravide reprezintă un factor de risc substanțial, fiind asociat cu o mortalitate ridicată, motiv pentru care sarcina este contraindicată la femeile care sunt diagnosticate cu această afecțiune. Modificările fiziopatologice induse de sarcină și naștere au efecte negative asupra vascularizației pulmonare și a funcției cordului drept. Vârsta tânără a femeii gravide, simptomele non-specifice sau formele asimptomatice, în special la debutul HAP, precum și lipsa monitorizării sarcinii pot duce la confuzii de diagnostic. La gravidele cu HAP, continuarea sarcinii implică constituirea unei echipe multidisciplinare pregatită pentru monitorizarea intrapartum, îngrijirea în timpul nașterii și urmărirea post-partum. În ciuda progreselor în tratamentul afecțiunii, ghidurile contraindică sarcina la pacientele cunoscute cu HTP. Succesul poate fi posibil apelând la echipe cu experiență, în centre de obstetrică înalt specializate.
Cuvinte-cheie: *hipertensiune arterială pulmonară (HAP), sarcină, naștere, tratament HAP, mortalitate peri- sau postnatală*

Introduction

Diagnosis of PAH is supported in cardiology and pulmonology departments, which have access to high-performance laboratory investigations: imagistic (HRCT), functional respiratory, including gaseous diffusion and experienced cardiac catheterization units. The treatment is performed in respiratory or cardiology specialist units. In recent years, significant progress has been made regarding treatment and monitoring patients with PAH. There are 6 National Treatment centers in Romania that run PAH programs: two in Bucharest, and one in each of the following cities: Iași, Cluj-Napoca, Târgu Mureș and Timișoara.

It is important that the obstetrician knows PAH personal history of the pregnant patient. If the woman wants to stay pregnant, despite recommendations, it is advisable to bring into her attention both mother and fetus vital risks, as well as the possibility to transmit the disease to the newborn, especially when we are dealing with heritable PAH. Genetic counseling and advice are desirable in these cases.

An undiagnosed, untreated pregnant woman, with unmonitored pregnancy coming into labor, represents a huge challenge, especially when she associates moderate or severe PAH forms with or without cardiac failure of the right heart. In these cases perinatal mortality is high, up to 50%, for which reason it is very important that the obstetrician should be aware of this pathology, and an experienced multidisciplinary team should be formed. When time permits, it is better that these cases should be guided to an experienced PH center[1,2].

The pulmonary circulation works as a system with low pressure and low vascular resistance in condition of high flow, totally different from systemic circulation. In a healthy young adult the mean pressure measured at end-expiration is 7-19 mmHg and the pulmonary vascular

resistance (PVR) is almost 1 mm Hg x min/L (1 Wood/unit)[3]. Anatomic and physiologic properties of pulmonary circulation allow adaptation to effort, as in certain *situ*ations such pregnancy. The compliance (pulmonary arterial vascular extensibility) and the ability to recruit new vascular territories prevent fluid from moving out from the vessels into the interstitial/ alveolar space, the entire cardiac output being accommodated by pulmonary circulation. Pregnancy and labor increase the demand on the heart - pulmonary system and could induce or worsen PAH through hemodynamic changes and hormonal factors[4].

The physiologic changes during pregnancy are: increase of sex hormone levels (human choriogonadotropin - hCG, estrogens and progesterone, which mediates vasodilator responses), increase of blood volume (almost 50-70%) especially after the 20th week, increase of the heart rate, stroke volume and cardiac output (CO), but decrease of systemic (SVR up to 40%) and pulmonary vascular resistances (PVR)[4-8]. The respiratory changes are also present: elevation of the diaphragm up to 4 cm with a decrease in functional residual capacity, increase of the tidal volume due to progesterone stimulation and appearance of airway edema[9-11]. Increase minute ventilation resultes in a respiratory alkalosis[11,12]. Not least, enlarging uterus with mechanical compression of the surrounding structures can affect heart and lung function[12].

Overview of PAH

Pulmonary Hypertension (PH) is a syndrome due to increased pressure in pulmonary circulation. It is defined by a mean pulmonary artery pressure ≥25 mm Hg at rest as assessed by right heart catheterization. Pulmonary Arterial Hypertension (PAH) includes a group of clinical conditions (from 5 major groups of PH disorders differentiated by WHO) which are more severe, progressive, associated with significant hemodynamic impairments, intense pulmonary vascular remodeling and increased pulmonary vascular resistance (PVR), more than 3 Wood units[12,13]. In time, it will associate right ventricle (RV) failure due to the inability of the pulmonary vasculature to adapt to the increased cardiac output and death[3]. Different from other types of PH (table 1)[12] the left sided heart filling pressure is normal (end-expiratory pulmonary artery wedge pressure is PAWP ≤15 mm Hg)[13]. PAH could be idiopathic or could be related to collagen vascular diseases, human immunodeficiency virus (HIV) infection, portal hypertension, drug and toxin exposure, congenital systemic-to-pulmonary shunts[15]. Depending on the mean pulmonary arterial pressure value that reflects the severity of hemodynamics, PAH can be classified in mild (PAPm between 24-40 mmHg), moderate (PAPm between 41-55 mmHg), and severe, with PAPm over 55 mmHg[3].

Epidemiology

Epidemiological data show that PAH is 2-3 times more common in women than in men and therefore the possibility of pregnancy should be considered in young and childbearing girls[16,17]. Idiopathic PAH is a rare disease: 1-2 cases in 1,000,000 inhabitants, rapidly progressive with a mean survival of only 2.8-3 years without treatment[2,18]. Latest data show an increase in survival (50% at 7 years) as a result of therapeutic progress[2,19,20]. PAH associated with other conditions is common in women of childbearing age: 30-50% in connective tissue disease (scleroderma, CREST syndrome, systemic lupus erythematous), 5-10% in congenital heart diseases, 0.7-3% in portal hypertension, 0.6% in HIV infection[3,21]. PAH associated with congenital heart diseases with relevant systemic-to-pulmonary shunts contribute to increase mortality (36% in Eisenmenger's syndrome). Mortality varies between 30% and 56% in PAH, according to retrospective review over 18 years until 1996. Late diagnosis of PAH, severe forms and late hospital admission for delivery were found independent predictive risk factors of maternal mortality[22,23].

Physiopathology

PAH is the result of association of vasoconstriction and obstructive vascular remodeling with the formation of plexiform and occlusive lesions, perivascular inflammation, enhanced extracellular matrix deposition and degradation. In those processes, vascular endothelial cells, smooth muscle cellule, fibroblasts, inflammatory cells are involved. Genetic abnormalities, epigenetic phenomena, altered microRNA function are involved[14,24]. Mutations in BMPR2 are frequent (80%) in families affected by heritable PAH. Remodeling process and increased vascular stiffness increase PVR leading to RV remodeling, RV failure, and death[14,24,25]. In pregnant PH patient, above-mentioned physiological changes of pregnancy can also influence and deteriorate the health. The major problem is the difficulty to accommodate increased cardiac output and circulating blood volume by the remodeled pulmonary vasculature.

Careful clinical examination may raise suspicion for PAH. Symptoms and signs of pulmonary hypertension in pregnant women are nonspecific (may be found in normal pregnancy): progressive dyspnea, fatigue and chest pain. The patients may associate right cardiac failure associated with bilateral ankle edema, pre-syncope, dizziness or syncope. Clinical exam reveals signs of right ventricular failure[26].

Investigation

Pregnant women already diagnosed with PAH need to be investigated for monitoring the hemodynamic status with increasing maternal age pregnancy, treatment monitoring and assessing the risk for complications. Chest X-ray and HRCT have limited indication due to radiation exposure. Right ventricular hypertrophy, right atrial enlargement, enlarged pulmonary arteries and pulmonary parenchymal abnormalities are better evaluated on HRCT[3]. ECG shows right axis deviation and right atrial and ventricular dilation. Echocardiography: due to changes in pregnancy, an over- or underestimated PAP in 30% pregnant patients may exist and lower blood viscosity leads to false increased tricuspid jet[27]. Asymptomatic pericardial effusion in up to 40% of wo-

men, and dilated right atrium (RA) and right ventricle (RV) could appear in normal pregnant women.

Right heart catheterization is the gold standard in diagnosing and it is especially indicated for patients admitted to the ICU with severe PH and RV failure, allowing the measurement of RA and pulmonary pressures, cardiac output and mixed venous oxygen saturation. The specific hemodynamic changes during pregnancy could influence the accuracy of results, due to catheter placement problems and determination of cardiac output[28].

Management

In PAH patients, continuation of the pregnancy involves establishing a specialist-run multidisciplinary team for monitoring and establishing intrapartum, delivery and postpartum management consisting of obstetricians, anesthesiologists, neonatologist, cardiologists, pulmonologists, rheumatologist and intensivists. The decisions regarding the delivery (where, when, and how), protocols for treatment and protocols for monitoring before, during and after delivery should be individualized to each patient.

Pregnancy management

All patients should be advised to discontinue pregnancy, using emergency contraception (misoprostol), therapeutic abortion in the first trimester and early delivery after[29,30]. However, permanent contraception should be taken into account, hysteroscopic sterilization being preferred instead of estrogencontaining contraception. Laparoscopic approach for tubal ligation is relatively contraindicated[29]. According to the guidelines, monitoring should be done monthly for the first 2 trimesters and weekly in the last quarter for patients who do not give up pregnancy[29]. The evaluation includes clinical examination, laboratory tests (brain natriuretic peptide), echocardiography, and 6minutewalk testing. Severe PAH is associated with higher maternal morbidity and adverse fetal outcome compared to pregnancy in women with mild PAH[31]. The aim of treatment is to maintain right ventricular function and reduce pulmonary vascular resistance. In this period, the therapy based on clinical status and severity of right heart damage is established opting either for oral phosphodiesters 5 inhibitors as sildenafil in mild forms, inhaled prostaglandins with iloprost in moderate forms or parenteral prostaglandins like intravenous (i.v.) epoprostenol in severe forms. Parenteral prostaglandins are not known to be teratogens and could be used for severe forms of PAH being potent pulmonary vasodilators[32,33]. Sildenafil is a phosphodiesterase 5 inhibitor which could be added or used as monotherapy in patients with normal RV function[34]. Calcium channel blocker therapy is allowed for patients who are not in a severe condition and meeting strict criteria for vasodilatorresponsive PAH. Endothelin receptor antagonists (ambrisentan, bosentan, macitentan) are contraindicated because of the known teratogenicity[35]. New therapies for PAH could improve the outcome. An increased risk for clinical deteriorations exists in weeks 11-12 and 20-24[29]. In case of worsening the health condition, we can choose a higher level of treatment or even termination of pregnancy. Induced or spontaneous abortion could happen. Furosemide, oxygen therapy, fluid restriction (1-2 L), lowsalt diet for avoiding cardiac decompensation can be used as diuretics[36]. Moreover, hypercoagulability state in pregnancy and thromboembolic risk that may worsen pregnancy further evolution should be taken into account. Low-molecular-weight heparin and unfractionated heparin during labor can be used in patients with risk (prolonged bed rest, venous stasis). Oral anticoagulants are contraindicated and they are stopped at the onset of pregnancy[29]. Before labor starts, we will discuss with the patient about the type of surgery and anesthesia, presenting the advantages and disadvantages of each method, depending on the patient's health.

Delivery

The studies showed that significant hemodynamic changes take place at the moment of delivery in normal patients due to fluid overload (the release of vena cava obstruction, auto-transfusion of blood from uterine contractions)[9,29]. Choosing type of delivery is also controversial. Both techniques have advantages and disadvantages. The advantages for vaginal delivery are: minimizing postsurgical fluid shifts, minimizing anesthetic risk, placenta delivery is less difficult, less thrombogenic, fewer bleeding complications and infections appear and the patient can start diuresis earlier. It should be performed in ICU or the operating room because of laborinduced vasovagal responses and Valsalva maneuver, which can lead to cardiopulmonary collapse or syncope. Sympathetic stimulation induced by pain, acidosis, hypercapnea or hypoxia and increase in maternal blood volume immediately after delivery contributes to hemodynamic instability during delivery. Epidural anesthesia should be considered for vaginal delivery. Triggers for vasovagal reaction or syncope must be avoided because they could have catastrophic consequences in PAH patients[37]. Cesarean section avoids pushing or prolonged labor, avoids uncontrolled hemorrhage and it could be better monitoring. According to the guidelines, scheduled Cesarean is preferred after fetus becomes viable (week 34 of pregnancy). During the intervention, risk factors that could trigger the right ventricle decompensation (hypoxia, hypercarbia, acidosis, arrhythmias, anemia, anxiety and pain) are being watched[29,38,39].

Anesthesia

Combined spinal-epidural anesthesia is preferred instead of spinal or general anesthesia because of no additional risk of hypotension and depress cardiac contractility[40,41]. The treatment goals during delivery are to maintain right atrial and systemic pressure, to monitor fluid balance, and to avoid volume overload, particularly in the first 48 hours[42]. Prostaglandins i.v. may be considered in patients who haven't been treated yet or follow the same PAH treatment as before. In these cases close monitoring is recommended[29].

Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in bold.
BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Monitoring postpartum PAH patients

During the first 24-72 hours post delivery, there is the highest risk for maternal morbidity and mortality.

Acute hemodynamic instability with RV failure is the main cause of death[38] followed by thromboembolism. Prophylactic anticoagulation is indicated. The studies showed the overall maternal mortality rate is 17% in the USA[43], 17% in China[44], between 10 and 20% in the UK despite specific treatment[43,45]. The mortality of women with Eisenmenger's syndrome is much higher[22,46]. Patients should be closely monitored for several days postpartum in an intensive care unit. Recovery after delivery may take several months.

Conclusions

Symptomatic or high-risk pregnant patients should be screened for PAH, performing clinical assessment, pulmonary function test including diffusion capacity for carbon monoxide, echocardiography.

The increased risk of peri- and postnatal mortality contraindicates pregnancy in women with PAH. However, the decision to continue pregnancy involves careful monitoring throughout pregnancy period by an experienced multidisciplinary team in specialized units. The use of new therapies in pregnant women with PAH may improve the success rate and prevent maternal fetal mortality. ■

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