Chapter from the book *Pulmonary Hypertension - From Bench Research to Clinical Challenges*

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1. Introduction

Pregnancy in women with pulmonary arterial hypertension (PAH) due to defined or unknown causes is associated with greatly increased maternal morbidity. Significant respiratory, cardiac, and hematologic adaptations occur during pregnancy that may exacerbate the hemodynamic consequences of PAH and may precipitate malignant dysrhythmias and acute right ventricular overload and failure. Because of these potentially fatal consequences, the European Society of Cardiology and the American College of Cardiology/American Heart Association dissuade conception in women with PAH and recommend termination should pregnancy occur (Oakley 2003). Recent reviews suggest that significant progress has been achieved in the treatment and management of PAH during pregnancy (Bedard 2009). From 1978 to 1996 the overall maternal mortality rate was 38% and declined to 25% from 1997 to 2007 (Bedard 2009). Despite this improvement, mortality rates remain significantly elevated and the consideration of pregnancy in women with PAH should be thoroughly reviewed and discussed prior to conception (Roberts 1990) and, for those women with PAH who become pregnant or are diagnosed with PAH during pregnancy, a multidisciplinary management team with expertise in high risk pregnancy, maternal-fetal medicine, and pulmonary hypertension is warranted (Kiely 2010).

In this chapter, we will review the maternal physiological changes that occur during pregnancy and their effects on pulmonary vascular and cardiac function, physical examination findings and diagnostic studies of PAH during pregnancy, the epidemiology and outcomes of pregnancy in women with PAH, and current pharmacologic and management strategies for the treatment of these patients.

2. Physiologic changes during pregnancy (Table 1)

2.1 Respiratory

Profound changes in respiratory physiology occur during pregnancy. Basal oxygen consumption increases by 50 ml/min by term (Thornberg 2000). This increased oxygen
demand is met by augmentation of minute ventilation. Alveolar ventilation increases due to progesterone, effects of reduced osmolality, increased angiotensin II and vasopressin (Thornberg 2000). The elevation in alveolar ventilation is caused primarily by a 25-40% increase in tidal volume (Fujitani 2005) and produces a fall in alveolar $P_{CO_2}$ from 38 torr to 30 torr at term (Thornberg 2000). The total lung capacity may decline slightly but does not change significantly during pregnancy. In contrast, functional residual capacity declines by 20-30% due to elevation of the diaphragm by the gravid uterus, reduced downward pull by the abdomen, and alterations in the chest wall that diminish outward recoil (Hegewald 2011).

Table 1. Physiologic Changes during Pregnancy

<table>
<thead>
<tr>
<th>Pulmonary</th>
<th></th>
<th>Cardiovascular</th>
<th></th>
<th>Hematologic</th>
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</thead>
<tbody>
<tr>
<td>Total Lung Capacity</td>
<td>Same to slightly decreased &lt;5%</td>
<td>Blood volume</td>
<td>Increases 50%</td>
<td>Levels of factors</td>
</tr>
<tr>
<td>Functional Residual Capacity</td>
<td>Decreases 20-30% (200-300 ml)</td>
<td>Systemic vascular resistance</td>
<td>Decreases 20%</td>
<td>II, V, VII, VIII, IX, X, XI,</td>
</tr>
<tr>
<td>Residual Volume</td>
<td>Decreases 20-25% (200-400 ml)</td>
<td>Pulmonary vascular resistance</td>
<td>Decreases 25%</td>
<td>fibrinogen and von Willebrand factor</td>
</tr>
<tr>
<td>Inspiratory Capacity</td>
<td>Increases 5-10% (200-350 ml)</td>
<td>Systolic blood pressure</td>
<td>Decreases 5-10 mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diastolic blood pressure</td>
<td>Decreases 10-15 mm Hg</td>
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<tr>
<td></td>
<td></td>
<td>Heart rate</td>
<td>Increases 10-15 bpm</td>
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<tr>
<td></td>
<td></td>
<td>Stroke volume</td>
<td>Increases</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Cardiac output</td>
<td>Increases 30-50%</td>
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<td></td>
<td></td>
<td>Left ventricular ejection fraction</td>
<td>Increases</td>
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<tr>
<td></td>
<td></td>
<td>Central venous pressure</td>
<td>Same</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Pulmonary pressures</td>
<td>Same</td>
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</table>

(adapted from Hegewald 2011, Hameed 2007)
2.2 Pulmonary vasculature

Blood volume expands up to 40% by term (Thornberg 2000) and most of the increase is due to plasma volume increases (Madden 2009). In addition, the red cell mass enlarges by 30% (Thornberg 2000). Cardiac output (CO) increases by more than 50% by mid-third trimester due to augmentation of stroke volume, quickened heart rate, reduced afterload, and increased left ventricular (LV) outflow area (Thornberg 2000, Capeless 1989, Duvekot 1994, Mashini 1987, Vered 1991). Heart rate accelerates gradually throughout gestation whereas engorgement of stroke volume (SV) stabilizes by 20 weeks (Atkins 1981). SV increases due to cardiac remodeling with enlargement of all four chambers, elevation in end diastolic volume, and maintenance of ejection fraction (Thornberg 2000, Fujitani 2005). Cross sectional echocardiographic studies of left ventricular mass and function demonstrate a greater than 50% increase in LV mass during pregnancy; LV diastolic function also increases during the first two trimesters but then declines during the last trimester (Kametas 2001). Despite the elevated CO, systolic and diastolic arterial blood pressure decline and pulse pressure widens slightly during pregnancy. With the increase in CO and decrease in blood pressure, peripheral vascular resistance declines over the first trimester and remains low for the remainder of pregnancy without further reduction. Aortic diameter and compliance, venous capacitance, and blood volume all increase (Thornberg 2000).

Although pulmonary blood flow increases dramatically during pregnancy, a reduction in pulmonary vascular resistance (PVR) maintains pulmonary arterial pressure (PAP) constant throughout pregnancy. Serial pulsed Doppler echocardiographic studies of 13 women during pregnancy demonstrated the mean PAP before pregnancy was 13.8 mm Hg and did not change throughout pregnancy; however, pulmonary blood flow increased from 4.88 to 7.19 L/min during pregnancy with a decline in pulmonary vascular resistance from 2.85 to 2.17 resistance units. PVR returned to normal by 6 months post partum. (Robson 1991)

CO may increase by 25-30% during the second stage of labor due to uterine contractions and by up to 80% immediately post partum due to autotransfusion of blood from the uterus to the systemic circulation (Madden 2009). Postpartum, heart rate, systemic vascular resistance, and cardiac output decrease and cardiac enlargement begins to regress. Blood volume normalizes quickly and hemodynamic parameters including cardiac output, stroke volume, ventricular volume, myocardial contractility, and pulmonary and systemic vascular resistance return to pre-pregnancy levels over several weeks whereas cardiac remodeling occurs over several months (Weiss 2000, Capeless 1991, Duvekot 1994).

2.3 Hematologic

There is a significant increase in procoagulant activity during pregnancy due to increases in clotting factor concentrations and decreases in quantity and activity of physiological anticoagulants (Brenner 2004). The levels of factors II, V, VII, VIII, IX, X, XII, fibrinogen and von Willebrand factor increase whereas protein S activity declines and resistance to activated protein C develops (Brenner 2004, Montavon 2008). There are also increases in circulating prothrombin fragments (PF1+2) and thrombin-antithrombin complexes. Microparticles shed from the cell membranes of maternal endothelial cells and platelets are also associated with enhanced thrombosis. Throughout pregnancy, the risk of venous
thrombosis is increased 4-10 fold and is 3-4 fold higher post partum compared with pregnancy (Brenner 2004, Montavon 2008). The platelet count generally decreases during pregnancy because of hemodilution and increased destruction (Thornton 2010). In women with pre-existing PAH, these hematologic changes may predispose to in situ thrombosis within the already deranged pulmonary vasculature exacerbating elevations in pulmonary vascular resistance and precipitating right ventricular strain and potentially failure.

3. History and physical examination

3.1 History
Cardiopulmonary symptoms are common throughout pregnancy. Progressive fatigue, weariness, and breathlessness frequently occur during pregnancy. Palpitations related to tachycardia are often experienced. Other common symptoms of pregnancy include pedal edema, fatigue, and reduced exercise tolerance (Hameed 2007). Supine hypotension may occur in up to 10% of pregnant women and may cause lightheadedness, dizziness, and occasionally syncope (Hameed 2007). The symptoms of PAH are very similar and may include exertional breathlessness or syncope, fatigue, dizziness, lower extremity edema, palpitations, chest discomfort, and tachycardia. The strong similarity between the clinical manifestations of normal pregnancy and the symptoms of PAH confound the recognition and diagnosis of PAH during pregnancy.

A careful clinical history helps to identify or exclude recognized causes of PAH. A thorough medication history including prior use of anorexigens or chemotherapeutic agents should be elicited (Rubin 2005). Serologies can establish prior exposures to HIV and hepatitis B and C. A history of prior or familial thrombosis should prompt consideration of chronic thromboembolic disease. Other pulmonary processes such as concurrent interstitial lung disease should be pursued with imaging studies such as high resolution chest computed tomography and pulmonary function testing. A thorough history of skin, joint, and muscle symptoms as well as serologic testing can determine the presence of a concurrent connective tissue disorder. A careful history and evaluation for congenital and acquired cardiac disorders should be considered because many women with PAH during pregnancy have known or undiagnosed cardiac disease.

3.2 Physical examination
Cardiac auscultatory changes are present in over 90% of pregnant women and are usually physiologic flow murmurs caused by cardiac dilation, increased blood volume, and elevated cardiac output. Tricuspid or pulmonic regurgitation occurs in over 90% of pregnant women and 28% have echocardiographic evidence of mitral regurgitation (Hameed 2007). Pregnancy-associated flow murmurs frequently occur during mid-systole and are present at the left lower sternal border and pulmonic areas (Hurst 1958, O’Rourke 1970). In women with PAH, signs of right ventricle enlargement or overload may include the presence of a right ventricular lift, prominent P2 right sided S4 gallop, and the murmur of tricuspid regurgitation. Tricuspid valve insufficiency may be manifest by elevated jugular venous pressure, hepatojugular reflux, and a pulsatile liver. Thus, the cardiac findings of normal pregnancy and PAH are very similar and the lack of distinguishing clinical features may delay further studies to diagnose the presence of elevated pulmonary pressures.
3.3 Electrocardiogram

PAH may cause right ventricular hypertrophy or strain which can be detected by electrocardiographic changes. The electrocardiographic manifestations of cor pulmonale are relatively specific, 86%, but not sensitive, 51%, for PAH and do not correlate with the severity of PAH (Oswald-Mammosser 1987; Himelman 1988). Electrocardiographic features that suggest PAH include: A) P pulmonale, P-wave amplitude > 2.5 mm in leads II, III, and/or aVF; B) S1, S2, S3 pattern; C) an S1 Q3 pattern; D) incomplete or complete right bundle branch block; E) evidence of RVH: R axis deviation ≥ 100°, dominant R wave in lead V1 ≥ 7 mm in amplitude, ST segment depression and T wave inversion in leads V1 to V4, and deep S waves in leads V5, V6, I and aVL with a QRS duration < 0.12 s; and F) low voltage QRS (Barbera et al 2003; Harrigan and Jones 2002). Pregnancy is associated with electrocardiographic changes that may obfuscate the electrocardiographic recognition of PAH: A) left axis deviation; B) reduced QRS voltage; C) T-wave inversion in lead III; D) Q-waves and inverted P-waves in lead III that may normalize with inspiration; E) sinus tachycardia; F) presence of premature atrial and ventricular beats; and G) other dysrhythmias (Hameed 2007). Thus, pregnancy-associated changes in the electrocardiogram may obscure the electrocardiographic manifestations of PAH, delaying or thwarting its recognition and diagnosis.

4. Effects of normal pregnancy related vascular changes on pre-existing PAH

PAH is associated with increased PAP due to elevated PVR caused by vascular remodeling and local thrombus formation that can produce cor pulmonale and RV failure. Individuals with pre-existing PAH have difficulty tolerating the physiologic changes of pregnancy especially the elevation of heart rate and circulating blood volume. CO may have been reduced by increased PVR and the right ventricle may not be able to increase output due to the elevated afterload. The subsequent decrease in left ventricular preload may further accentuate the decline in systemic blood pressure due to an inability to compensate for the reduction in SVR that occurs during pregnancy. The fixed pulmonary vasculature of PAH may preclude or attenuate the physiologic decline in PVR that occurs during pregnancy to accommodate the increase in pulmonary blood volume and flow. Any augmentation of PVR (due to in situ or metastatic pulmonary vascular thrombosis, hypoxemia, acidosis, or hypercarbia) increases RV work and may trigger pulmonary hypertensive crisis, RV failure, acute reduction in LV preload, and precipitous reduction in systemic blood pressure (Warnes 2004, Madden 2009).

Pregnancy-related physiologic changes in coagulation may accentuate in situ thrombosis within the pulmonary vasculature or pulmonary emboli that may further impede pulmonary blood flow and precipitate a critical reduction in RV function and systemic hypotension (Madden 2009).

Diagnosis of unrecognized PAH during pregnancy may be difficult as many of the cardiac changes of pregnancy may mask or mimic the findings of PAH. The presence of PAH may be manifest by signs and symptoms of right heart failure, PAH crisis with acute RV failure, dysrhythmias, and pulmonary thromboembolic disease. Exertional breathlessness out of proportion to that expected during pregnancy may be the sole symptom of PAH. The differential diagnosis includes pre-existing cardiac abnormalities, patent foramen ovale, asthma, peripartum cardiomyopathy, and thromboembolic disease.
5. Screening for PAH before or during pregnancy

A retrospective review of 27 patients undergoing echocardiography and right heart catheterization (RHC) during pregnancy from 1990 to 2000 showed that echocardiography significantly over-estimated the presence and severity of PAH (Penning 2001). Over three quarters of these patients had structural heart defects and most were due to congenital cardiac disease. Nearly one third of patients with PAH estimated by echocardiography had normal pressures at the time of RHC. This overestimation of the presence of PAH by echocardiography may be due to the methodology used to calculate PAP: the gradient between the right atrium and right ventricle was determined using the modified Bernoulli equation, \(4v^2\), and the right atrial pressure was estimated from the degree of collapse of the inferior vena cava (IVC) during inspiration (Hemnes 2009). However, the increase in blood volume during pregnancy may reduce respiratory variation in IVC diameter and lead to overestimation of right atrial (RA) pressure causing the calculated PAP to be falsely elevated. The average sPAP (systolic PAP) determined echocardiographically was 59.6 mm Hg but was only 54.8 when measured hemodynamically (p<0.005). In another study of 18 patients undergoing RHC and echocardiography, one third of patients diagnosed with PAH by echocardiography had normal pressures on RHC. Although the echocardiographically estimated sPAP was 66.3 mm Hg and the average sPAP measured at RHC was 62.7 mm Hg, the two measurements correlated significantly. These studies show that Doppler echocardiography is not specific for the determination of PAH and up to one third of individuals with elevated PAP’s by echocardiography may have normal pulmonary pressures measured by RHC. Thus, invasive hemodynamic measurement is essential for the diagnosis and subsequent management of PAH during pregnancy.

6. Preconception counseling

6.1 Clinical outcomes: Morbidity and mortality-maternal and fetus

In a systemic review of 73 pregnant women with PAH from 1997 to 2007, 29 (40%) had idiopathic PAH, 29 (40%) had PAH associated with congenital heart disease, and 15 (21%) had other causes of PAH (Bedard 2009). The diagnosis of idiopathic PAH was known prior to pregnancy in only 45% of the women, whereas over 75% of women with other causes of PAH were known to have PAH prior to conception. Of those with idiopathic PAH, the mortality rate was 17%, 2 died during pregnancy and 3 died post partum. The causes of death included refractory right heart failure, circulatory collapse, and PAH crisis. Of those with PAH associated with congenital heart disease, 8 (28%) died during the post partum period due to right heart failure, pulmonary thromboembolism (PTE), cardiac arrest, PAH crisis, and bacterial endocarditis. Five patients (33%) with other causes of PAH died, 1 during pregnancy and 4 post partum. Right heart failure and PTE were the major causes of death. Neonatal or fetal death occurred in 9.6% and premature delivery occurred in nearly all pregnancies.

7. Management of pulmonary hypertension during pregnancy

7.1 General medical management

Currently, there are no clear consensus guidelines for the management of PAH in pregnancy; however, several case series have been published in the last two decades that provide guidance for the evaluation, treatment, and monitoring of this high risk patient
group. If PAH is suspected, a thorough evaluation should ensue. RHC is required for definitive confirmation of the diagnosis of PAH as well as the assessment of disease severity (McLaughlin 2009). A multidisciplinary team approach to the care of PAH in pregnancy has been utilized successfully (Garabedian 2010). This approach is associated with improved survival compared with historical data (Kiely 2010, Smedstad 1994). The multidisciplinary team includes physicians and staff with expertise in pulmonary vascular disease, hematology, maternal-fetal medicine, high risk obstetrics, and obstetric anesthesia.

The pharmacotherapeutic management of PAH requires a multifaceted approach with the goal of lowering RV afterload by reducing pulmonary vascular resistance, prevention of thromboembolism, optimization of RV preload, and maintenance of RV inotropy. Initial pharmacologic management utilizes pulmonary vasodilators to reduce RV afterload. Several pulmonary vasodilators are currently approved for the medical management of PAH; however, all therapeutic options for PAH are not advisable for use in patients during pregnancy because of the teratogenicity of selected agents. (Figure 1)

7.2 PAH specific therapy with pulmonary vasodilators

PAH occurs due to an imbalance of pulmonary vasodilatory and constrictor mediators in the pulmonary vasculature causing vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis in situ (Voelkel 1997). Aberrations of many physiologic pathways likely contribute to these pulmonary vascular changes and the subsequent development of pulmonary hypertension. Three of these pathways are targets for currently approved PAH therapies and include the endothelin, prostacyclin, and nitric oxide pathways (Humbert 2004).

Endothelin is a potent pulmonary vasoconstrictor (Yanisagawa 1988). Endothelin receptor antagonists (ERAs) improve outcomes in non-pregnant pulmonary arterial hypertension patients (Rubin 2002, Galiè 2008); however, the use of ERAs is not recommended for treatment of PAH in pregnancy because of their known teratogenicity (pregnancy risk category X).

Prostacyclin is a potent pulmonary vasodilator with anti-proliferative (Clapp 2002) and anti-thrombotic effects (Moncada 1976). The prostacyclin analog, epoprostenol, was the first available PAH specific therapy and has been shown to improve functionality, pulmonary hemodynamics, and survival in non-pregnant PAH patients (Barst 1996). Epoprostenol is the most frequently reported treatment for PAH in pregnancy (Bédard 2009). Epoprostenol is classified as a pregnancy risk category B drug and has not been associated with fetal abnormalities in recent literature reviews (Stewart 2001, Bédard 2009, Kiely 2010). More recently approved prostacyclin analogues include treprostinil and iloprost. Treprostinil carries a pregnancy category B risk classification with limited data regarding safety data in pregnancy. Iloprost has been shown to be associated with adverse fetal effects in animals (pregnancy risk category C) but has been used successfully without adverse human fetal effects in a series of 9 patients (Kiely 2010).

Nitric oxide is a known pulmonary vasodilator (Pepke-Zaba 1991). The nitric oxide pathway can be targeted for the treatment of pulmonary hypertension by exogenous delivery of nitric oxide or augmentation of nitric oxide dependent cyclic GMP mediated pulmonary vasodilation by inhibiting the breakdown of cyclic GMP by phosphodiesterase type 5 (PDEI-5) (Humbert 2004). Phosphodiesterase inhibition with sildenafil has been used to treat
PAH in pregnancy with no reported complications (Goland 2010, Kiely 2010). The currently approved PDEI-5s for the treatment of PAH are pregnancy risk category B.

Over the last two decades, multiple clinical series and case reports have described outcomes and management of PAH in pregnancy. A systematic review of the published literature from 1997 to 2007 found 47 case reports with a total of 73 parturients affected by PAH (Bédard 2009). Advanced PAH therapies were utilized in 72% of the reported patients. Prostacyclin analogues were the most commonly used form of PAH therapy. In patients with idiopathic PAH treated with epoprostenol, the mortality rate was 20% (Bédard 2009). Overall mortality in PAH patients managed from 1978-96 compared with patients managed from 1997-2007 has improved. Mortality has decreased in patients with idiopathic PAH (30% to 17%), congenital heart disease associated PAH (36% to 28%) and other forms of precapillary PAH (56% to 33%) in the modern era (P = 0.047) (Bédard 2009).

Prior to the initiation of pharmacologic treatment, detailed discussion of the risks and benefits of the various therapeutic options should be undertaken. Based upon the current available literature, initiation of a prostacyclin with careful upward titration of the dose as tolerated is advisable (Bédard 2009, Kiely 2010, Garabedian 2010). The addition of oral sildenafil has been used successfully in the past and could be considered adjunctive therapy (Goland 2010, Kiely 2010).

### 7.3 Maternal and fetal monitoring

The optimal monitoring strategy for PAH in pregnancy is unclear at the present time. Initial evaluation and commencement of PAH therapy, i.e. prostacyclin, likely will require observation in the inpatient setting or prolonged intense monitoring as an outpatient. Subsequently, close outpatient monitoring may be considered in the appropriate patient. Successful outpatient monitoring has been reported in a series of 9 women with PAH during 10 pregnancies managed at a quaternary care hospital in the United Kingdom (Kiely 2010). These patients were evaluated in the outpatient setting every 4 weeks until week 28 gestation followed by every 2 weeks until week 30 gestation and then weekly until 24 hours prior to scheduled delivery unless clinical worsening occurred that required hospitalization. Each outpatient assessment included a history, examination, routine laboratory assessment, electrocardiogram, and an exercise tolerance assessment. Maternal cardiac echocardiogram was repeated if clinically indicated (Kiely 2010). Once hospitalized, continuous monitoring of maternal heart rate and oxygen saturation was performed in all patients. Repeat right heart catheterization remains debatable and is not universally utilized during pregnancy for evaluation of clinical worsening and/or at the time of delivery (Kiely 2010, Bonnin 2005).

In a systematic review of outcomes in PAH in pregnancy from 1978-1996 the overall neonatal survival ranged from 87% to 89% (Weiss 1998). Fetal monitoring and ultrasound biometry (Garabedian 2010, Kiely 2010) often is utilized to monitor fetal growth and development. If a fetal abnormality or growth restriction is suspected, further assessment is employed to guide management (Kiely 2010).

### 7.4 Thromboprophylaxis

Pregnancy is a hypercoagulable state (Brenner 2004) associated with an increased risk of thromboembolic disease. Currently, there is no standard thromboprophylaxis regimen
recommended in PAH patients during pregnancy prior to delivery. Anticoagulation risks and benefits should be assessed on an individual basis and may not be well tolerated in select patient groups such as those with Eisenmenger's Syndrome (Pitts 1977) or other bleeding diatheses. Warfarin use is contraindicated in pregnancy due to its known teratogenicity (pregnancy risk category X.) Both unfractionated heparin (Bédard 2009) and low molecular weight heparin (LMWH) (Kiely 2010, Goland 2010, Garabedian 2010) have been successfully used for thromboprophylaxis and treatment in pregnant PAH patients. If full dose anticoagulation is chosen, transition to prophylactic dosing should occur prior to delivery and may be resumed after delivery if there is no contraindication (Kiely 2010).

7.5 Maintenance of optimal preload and management of anemia

Volume status should be monitored closely and maintenance of euvolemia should be attempted (Piazza 2005). Diuretic therapy may be necessary (Bédard 2009) but should be used with caution during the peripartum period when patients are at risk for rapid volume shifts and acute hemorrhagic anemia. If acute hemorrhage occurs, addressing the underlying cause and resuscitation is paramount to maintain hemodynamic stability (Krasuski 2004). If induction of labor is required, oxytocin, prostaglandin F2α should be infused slowly and intravenous boluses avoided because they may induce pulmonary vasoconstriction (Dagher 1993, Pinder 2002) which would be poorly tolerated.

7.6 Inotropic support

The third trimester of pregnancy, labor, and delivery are associated with a marked increase in cardiac work (Madden 2009). In women with PAH, the already taxed RV may not be able to meet these demands. Management of RV failure in this setting may require urgent delivery, dose escalation of pulmonary vasodilators to reduce RV afterload, and possibly direct inotropic support (Piazza 2005).

8. Timing of labor and mode of delivery

Timing of delivery is usually based upon the maternal and fetal tolerance of pregnancy. The risk for maternal deterioration increases as pregnancy progresses and is greatest after the majority of pregnancy-induced hemodynamic changes have occurred (approximately the 20th to 24th week of gestation) (Cheek 2001). Frequently, delivery is preterm either due to maternal worsening or planned delivery at 32-34 weeks gestation (Bédard 2009, Kiely 2010).

The optimal mode of labor and delivery remains unclear in patients with PAH and should be tailored to fit the individual patient’s needs. A review of 15 consecutive pregnancies in women with PAH managed at a referral center in France from 1992 - 2002 revealed an overall mortality of 36% and there was not a clear survival advantage associated with any particular mode of delivery. Scheduled cesarean section delivery with regional anesthesia via epidural or spinal-epidural is reported as the preferred delivery mode in two series. The advantages of this approach are daytime scheduling and avoidance of marked hemodynamic changes that may occur with vaginal delivery and general anesthesia (Bonnin
Regional anesthesia with cesarean section has been used successfully in several other reported cases (Bédard 2009, Khan 1996, Stewart 2001, Goland 2010). If epidural or spinal-epidural anesthesia is chosen, incrementally increasing epidural anesthesia is advocated to avoid rapid hemodynamic changes (Smedstad 1994). Additionally, the use of bolus spinal anesthesia is not recommended due to the potential for hemodynamic compromise.

Vaginal delivery without epidural anesthesia may not be well tolerated as it is associated with dramatic increases in cardiac work due to 12% increases in cardiac output in the first stages of labor and 34% in advanced labor at full cervical dilatation (Hunter 1992). If vaginal delivery is the chosen mode, epidural anesthesia with low-dose analgesia is recommended to reduce the adverse hemodynamic demands of labor (Slomka 1988, Smedstad 1994). Furthermore, if oxytocin, prostaglandin F$_{2\alpha}$ is used to induce labor it should be infused slowly to prevent the negative hemodynamic consequences caused by its pulmonary vasoconstrictive properties (Slomka 1988).

General anesthesia has been used successfully in the delivery of patients with PAH (Garabedian 2010, Bonnin 2005); however, general anesthesia may be associated with pulmonary vasoconstriction and other adverse hemodynamic changes associated with mechanical ventilation that may be deleterious in this patient population (Blaise 2003).

### 9. Post partum management

The postpartum period is the most critical time for pregnant PAH patients because the risk of morbidity and mortality is greatest due to a marked increase in pulmonary vascular resistance and cardiac output (Madden 2009). The majority of these hemodynamic alterations resolve in the first 2 weeks after delivery with complete normalization over the next 6 months (Cheek 2001). Monitoring post partum patients with PAH in a critical care setting is advocated for at least several days (Bonnin 2005) to a week (Kiely 2010) after delivery to ensure continued stability. Close monitoring with further escalation of pulmonary vasodilators, addition of inotropic support, and packed red blood cell transfusions may be required during this vulnerable time. The use of full dose anticoagulation is widely utilized in the post partum period and initiated 12-24 hours post partum based on the mode of delivery if there is no contraindication (James 2006).

Once the patient with PAH has been monitored and durable hemodynamic stability achieved postpartum, she can be maintained on appropriate PAH therapies (McLaughlin 2009) and discharged from the hospital with continued management in the outpatient setting (Kiely 2010).

### 10. Summary

Despite moderate advances in the management of PAH, pregnancy with concurrent PAH remains extremely high risk with significant morbidity and mortality (Bonnin 2005). Counseling regarding risks of pregnancy and early termination remain the recommended interventions. If a woman with PAH chooses to proceed with pregnancy, a detailed discussion of risks should be undertaken. Thorough evaluation and management utilizing a multi-professional team (Kiely 2010, Smedstad 1994) and full diagnostic assessment of PAH is recommended.
Suspect PAH
- Thorough evaluation under the care of a multi-professional team with expertise in management of PAH and high risk obstetrics

RHC
- Confirm the diagnosis of PAH
- Assessment of severity

PAH therapy
- Initiate and maintain PAH therapy with goal of lowering pulmonary vascular resistance and allowing improved tolerance of hemodynamic physiologic changes of pregnancy

Monitoring
- Outpatient setting if clinically appropriate
- Inpatient if clinical worsening/hemodynamic instability and prior to delivery

Delivery
- Mode of delivery selected based on individual patient characteristics
- Possible hemodynamic benefit from planned cesarean section with regional anesthesia

Postpartum
- Inpatient monitoring in the critical care setting
- Significant risk for hemodynamic compromise in the post-delivery period

Fig. 1. Right heart catheterization (RHC), Pulmonary arterial hypertension (PAH)
PAH therapy should be initiated and gradually increased to maintain hemodynamic stability. Inpatient monitoring is recommended in cases of worsening and prior to scheduled delivery (Kiely 2010). The optimal mode of delivery is not clear at this time but scheduled cesarean section with regional anesthesia has been used successfully in multiple case reports (Bédard 2009, Khan 1996, Stewart 2001, Goland 2010). The post partum period is the most critical time for worsening and death because of the rapid reversal of the physiologic hemodynamic changes of pregnancy. As these alterations resolve, post partum patients with PAH should be monitored in a critical care setting for several days to a week after delivery and supported medically. After discharge, continued close monitoring is recommended as women with PAH are at risk for decompensation for several months after delivery.

11. References


Pregnancy and Pulmonary Arterial Hypertension

303


The textbook "Pulmonary Hypertension - From Bench Research to Clinical Challenges" addresses the following topics: structure and function of the normal pulmonary vasculature; disregulated cellular pathways seen in experimental and human pulmonary hypertension; clinical aspects of pulmonary hypertension in general; presentation of several specific forms of pulmonary hypertension, and management of pulmonary hypertension in special circumstances. The textbook is unique in that it combines pulmonary and cardiac physiology and pathophysiology with clinical aspects of the disease. First two sections are reserved for the basic knowledge and the recent discoveries related to structure and cellular function of the pulmonary vasculature. The chapters also describe disregulated pathways known to be affected in pulmonary hypertension. A special section deals with the effects of hypoxia on the pulmonary vasculature and the myocardium. Other three sections introduce the methods of evaluating pulmonary hypertension to the reader. The chapters present several forms of pulmonary hypertension which are particularly challenging in clinical practice (such as pulmonary arterial hypertension associated with systemic sclerosis), and lastly, they address special considerations regarding management of pulmonary hypertension in certain clinical scenarios such as pulmonary hypertension in the critically ill.

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