Case Report

Current Opinion in Gynecology and Obstetrics Pulmonary Arterial Hypertension in Pregnancy: Outline of Multidisciplinary Care

Patel MB¹, Kellerhals S², Horton JP², Fisher MR³, Krishna I¹ and Badell ML^{1*}

¹Department of Gynecology and Obstetrics, Division of Maternal-Fetal Medicine, Emory University School of Medicine, Atlanta, USA

²Department of Gynecology and Obstetrics, Division of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, USA

³Emory University School of Medicine, Department of Medicine, Division of Pulmonary, Allergy, Sleep, and Critical Care, Atlanta, USA

***Correspondence:** Martina L. Badell, 15th floor Emory Perinatal Center, Emory University Hospital Midtown, 550 Peachtree Street, Atlanta, GA 30308; Tel: 404-686-2433; Fax: 404-686-2015; E-mail : mbadell@emory.edu

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Abstract

Pulmonary Arterial Hypertension in pregnancy causes significant maternal and fetal morbidity. There is currently no consensus on recommendations for overall management in pregnancies complicated by pulmonary arterial hypertension. We recommend institutions help build a multidisciplinary team with knowledge about pulmonary arterial hypertension to coordinate care during pregnancy, at delivery and in the postpartum period. The purpose of this article is to highlight some of the challenges in caring for these women, review the literature and help guide care teams by outlining our management process for 5 pregnant patients with WHO Group 1 pulmonary arterial hypertension on epoprostenol.

Introduction

Pulmonary arterial hypertension (PAH) in pregnancy and in the postpartum period has been associated with a 25-56% risk of maternal mortality [1,2]. Pulmonary hypertension develops from a wide range of disease processes and has varying degrees of severity. There are many factors that modulate this high mortality risk such as the severity of PAH noted on echocardiogram, history of myocardial infarction or cerebrovascular event, presence of valvular heart disease or the presence of right heart failure. The most severe risk of mortality associated with PAH in pregnancy is the development of Eisenmenger's syndrome which carries a mortality risk of up to 50% [3]. Although considered a contraindication to pregnancy, some reproductive-age women with PAH elect to pursue/continue pregnancy or are diagnosed with PAH during pregnancy. There must be multidisciplinary care

throughout the pregnancy of a woman with PAH with obstetric, pulmonology, critical care, cardiology, and neonatology teams [3,4]. During the management of the cases reviewed below, our center established guidelines and checklists for the initiation and coordination of a multidisciplinary care team. We believe this approach at our center has led to improvements in maternal and fetal outcomes. Additionally it provides the clinical team with a framework to know they are caring for these complex patients with support. This manuscript seeks to review and suggest a multidisciplinary management strategy for pregnancy, delivery, and the postpartum period based on experiences in our tertiary care center caring for 5 pregnant patients with pulmonary arterial hypertension WHO Group 1 on epoprostenol.

Classes of pulmonary arterial hypertension

The definition of pulmonary hypertension has evolved over the years since the first consensus definition was proposed in 1973 [5]. The current definition of pulmonary hypertension, updated in 2018, is a mean pulmonary artery pressure of greater than 20 mmHg at rest [6]. This term encompasses a wide range of disease processes which are classified by the World Health Organization (WHO) into 5 groups based on etiology. Group 1 is PAH and includes multiple subcategories such as idiopathic PAH, heritable PAH, drug and toxin induced PAH, PAH associated with other diseases (such as connective tissue disease, HIV, etc.). Group 2 is pulmonary hypertension due to left heart disease, Group 3 is pulmonary hypertension due to lung disease and/or hypoxia, Group 4 is PH due to pulmonary artery obstructions and Group 5 is pulmonary hypertension with unclear and/or multifactorial mechanisms. The distinction between Groups 1-5 and subcategories within them is very important as prognosis and treatment can vary widely. The cases described below and the approach to management are specific to PAH (WHO Group 1 disease). With the advent of new treatments for PAH, including the use of the prostacyclin epoprostenol, successful management during pregnancy has led to improved survival [7].

Pathophysiology of pulmonary arterial hypertension

In pregnancies that are not complicated by pulmonary hypertension, the pulmonary vasculature decreases its vascular resistance to accommodate the normal physiologic increase in cardiac output by both vasodilation and recruitment of previously non-perfused vessels. In patients with pulmonary hypertension, this normal compensatory response is decreased or absent. Given the linear rise in pulmonary artery pressure with increases in cardiac output in these patients, normal physiologic changes can lead to increased right ventricular strain and right heart failure. This heart failure can lead to a chronic state of hypotension, reduced cardiac output, and hypoxemia. Patients with pulmonary hypertension in pregnancy most often deteriorate between weeks 20-24 given that this is the period during which the most pregnancy-related hemodynamic changes occur [4]. The intrapartum and postpartum periods are also a time of significant risk due to the effects of pain on the cardiovascular system as well as the fluid shifts associated with labor and delivery [8]. Dyspnea with exertion or with rest, dizziness, syncope, chest pain, and edema are common presenting symptoms of

pulmonary hypertension. In a review of 49 cases of pulmonary hypertension in pregnancy, they found that women with severe pulmonary hypertension needed advanced therapy which included inotropes, pulmonary vasodilators, and ECMO in 73% of cases [9].

Epoprostenol use in pregnancy

Available therapies for pulmonary hypertension include endothelin receptor antagonists, phosphodiesterase 5 inhibitors, soluble guanylate cyclase stimulators, calcium-channel blockers, and prostacyclins. Due to incidence of congenital malformations in animal studies, endothelin receptor antagonists are contraindicated in pregnancy. Calcium channel blockers can be a highly effective therapy for the rare patient that is an acute vasodilator responder. However, the majority of patients does not respond or lose their response over time and these therapies can cause significant hemodynamic deterioration when used inappropriately. Nitric oxide and sildenafil have been used during the intrapartum course for acute management of pulmonary hypertension [10].

Epoprostenol is a naturally occurring prostacyclin and vasodilator and the advanced therapy that has been best studied for the treatment of PAH. Its efficacy has been well-demonstrated in the non-pregnant patient and considered first line therapy in patients with severe disease [11]. While no randomized-controlled trials exist for its use in pregnancy, reproductive animal studies have shown no fetal harm at higher doses than recommended for use in humans [1]. To date, 14 case reports of epoprostenol use in pregnancy with therapy most often being initiated near the time of delivery. There have been two maternal deaths reported in patients treated with epoprostenol. In both of these cases, the patients presented with advanced right-ventricular failure, which progressed despite treatment. In all other cases, patients were successfully treated with no significant postpartum complications [12].

Due to its short half-life, continuous administration of prostacyclins is necessary. Epoprostenol is administered intravenously at an initial rate of 2-4 ng/kg/minute with dose adjusted as needed based on patient symptoms and follow-up hemodynamic and functional assessments. In general parenteral therapy is recommended during pregnancy due to its ease of titration. This medication is given via a pump which requires very specialized training and supplies. Part of our care team involved ensuring patients had safe access to this medication with appropriate nursing back-up.

Epoprostenol has not been shown to have any adverse neonatal effects. It is known to cause dilation of the fetal ductus arteriosus, however, due to its short half-life there are unlikely to be any post-natal effects. Consistent with other case reports of epoprostenol use, there were no adverse neonatal effects in the five cases described in our institution. No studies exist regarding epoprostenol use in the setting of lactation. However, given that epoprostenol is not orally active there are likely no effects to the infant from its maternal use during breastfeeding [10].

Preconception

Due to the associated high mortality rate, pulmonary hypertension is a contraindication to pregnancy and patients should be counseled regarding permanent methods of contraception. Patients with known pulmonary hypertension who become pregnant should be counseled extensively regarding the risks of pregnancy and should be offered pregnancy termination. The CARPREG II scoring system was published in 2018 and can be a clinically useful tool in predicting maternal morbidity and mortality in women with known cardiac disease. This scoring tool incorporates echocardiography findings, prior adverse cardiac events, and lesion-specific risks, including existing pulmonary hypertension to give an overall risk of adverse cardiac events during pregnancy which can be incorporated into comprehensive counseling [13]. In women with pulmonary hypertension who elect to pursue pregnancy after appropriate counseling, perinatal outcomes are better after one year of successful therapy with optimization of right-ventricular function prior to conception [8]. Women with idiopathic or heritable pulmonary hypertension should undergo genetic counseling regarding potential genetic outcomes for the pregnancy.

Case Presentations

We cared for 5 pregnant patients with PAH requiring epoprostenol during pregnancy at our institution between 2016-2018 (Table 1).

Case 1

34y G3P1011 presented at 9w1d with PAH associated with HIV (WHO functional class III). Prior to presentation she was already receiving epoprostenol via Hickman catheter and her dose was titrated throughout pregnancy. Her pregnancy was complicated by fetal growth restriction. She underwent a scheduled repeat cesarean section at 34w3d and tolerated the procedure well and was transferred out of the ICU on postpartum day 4 and discharged home on postpartum day 7. At one

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year follow up, she and baby were doing well and she has remained on epoprostenol therapy.

Case 2

30y G2P1001 at 30w5d transferred from an outside facility with shortness of breath and dizziness and was found to have pulmonary hypertension on echocardiogram. She was in acute right-sided heart failure (WHO functional class IV) complicated by hypoxemia due to shunting through a patent foramen ovale. She underwent a rapid evaluation and confirmation of her pulmonary arterial hypertension with a right heart catheterization. She received a Hickman catheter and was initiated on epoprostenol therapy. Pregnancy was complicated by fetal growth restriction with abnormal umbilical artery Dopplers. She went into preterm labor at 34 weeks and was delivered via repeat cesarean. She had venous and arterial access obtained for possible emergent ECMO cannulation at the time of delivery. She tolerated the procedure well and was transferred from the ICU on postoperative day 8 and discharged home on postoperative day 16. At one year follow up she and baby were doing well and she has remained on IV epoprostenol therapy.

Case 3

32y G2P0020 with a history of idiopathic pulmonary arterial hypertension (WHO functional class III) presented for preconception counseling and subsequently became pregnant. She was transitioned from oral treprostinil to IV epoprostenol at 19 weeks gestation. She remained stable and underwent an uncomplicated primary cesarean section at 35w1d. She tolerated the procedure well and was transferred out of the ICU on postoperative day 3 and discharged home on postoperative day 4. At her follow up, she was noted to be stable and resumed her oral treprostinil.

Case 4

33y G2P0010 at 31w4d presented as a transfer from an outside hospital after presenting with shortness of breath and lower extremity swelling and underwent a work up notable for pulmonary hypertension. Her urine drug screen at the outside facility was notable for amphetamines and the etiology of her PAH was thought to be drug induced. Her pregnancy was complicated by a shortened cervix for which she had a cerclage in place. She was started on IV epoprostenol. She went into preterm labor at 31w6d and subsequently underwent an urgent primary cesarean section. She tolerated the procedure well and was transferred out of the ICU on postoperative

day 6 and discharged home on postoperative day 7. At her 6 month follow up the patient was doing well and continued on IV epoprostenol.

Case 5

23y G2P0010 at 12w5d presented with history of PAH associated with Systemic Lupus Erythematosus (SLE) with concern for lupus nephritis (WHO functional class II). She underwent Hickman catheter placement at 28w3d and was initiated on epoprostenol therapy. She progressed to WHO functional class III during the pregnancy. She underwent a scheduled primary cesarean section at 34w3d without complications. She was discharged home from the ICU on postoperative day 4. At her 4 month follow up visit, she was doing well and is being weaned off of epoprostenol after re-initiation of dual oral therapy.

Antepartum management

Prenatal care should be initiated early in pregnancy and baseline assessment should include standard obstetric labs, ultrasound for dating, maternal echocardiography, brain natriuretic peptide measurements, and 6-minute walking test. Table 2 outlines recommended antenatal care per trimester. Intrauterine growth restriction is often seen as a result of chronic placental hypoperfusion and serial ultrasounds to assess fetal growth are recommended. Additional risks include stillbirth, preterm

delivery, and neonatal death and thus these patients warrant antenatal testing in the 3rd trimester [14]. Patients should be counseled extensively on the risks of pregnancy continuation utilizing one of the standardized and validated risk assessment modalities (ex: CARPREG I or II, WHO, NYHA Classification). The CARPREG II scoring system was published in 2018 and can be a clinically useful tool in predicting maternal morbidity and mortality in women with known cardiac disease. This scoring tool incorporates echocardiography findings, prior adverse cardiac events, and lesion- specific risks, including existing pulmonary hypertension to given an overall risk of adverse cardiac events during pregnancy which can be incorporated into comprehensive counseling [13]. We opted to use the WHO classification rather than the other cardiac risk assessment tools as they were primarily developed to predict cardiac outcomes in pregnancy in women with congenital cardiac disease. The WHO classification is listed for each patient in table 1.

The complexity of these cases and the multidisciplinary teams involved in the care of these patients requires clear communication for successful outcomes and the safety of each patient. Due to the high likelihood of cardiopulmonary resuscitation needed in the event of an emergency, the decision was made to have each patient present to the emergency department instead of labor

Table 1: Maternal cases of pulmonary arterial hypertension in pregnancy.

Mother	WHO Functional Classification at time of delivery*	PAH type	GA Epoprostenol Initiated	GA Delivery, method of delivery	Maternal Outcome	Neonatal Outcome (weight, APGARs)
1	III	HIV associated	Pre-pregnancy	34w3d, repeat cesarean section	Doing well at 1 year follow up on Epoprostenol therapy	1810g, 6/8
2	IV	Idiopathic	30w5d	34w, repeat cesarean section	Doing well at 1yr follow up on continued IV Epoprostenol therapy	1480g, 6/8
3	III	Idiopathic	19w0d	35w1d, elective primary cesarean section	Doing well at follow up and resumed oral treprostamol	2580g, 8/8
4	IV	Drug induced	31w5d	30w6d, primary cesarean section	Follow up at 6 months, doing well, continues on IV Epoprostenol	2200g, 4/6/8
5	III	SLE associated	28w3d	34w3d, primary cesarean section	Follow up at 4 months, doing well, weaning off of IV Epoprostenol	1925g, 9/9

*WHO classification definitions

and delivery for any non-scheduled hospital visit. The first person to be notified regarding the patient's presence in the hospital was the Obstetric Rapid Response team who notified Maternal-Fetal Medicine (MFM) and/or the pulmonology team and the communication tree was activated as listed in figure 1. The patient should meet members on the care team and be advised of signs/symptoms that would prompt hospital presentation. We recommend an assigned care team is established and table 3 outlines the physicians, nurses and support staff recommended to help coordinate care.

Figure 1: Pulmonary hypertension phone tree for pregnant patients with pulmonary arterial hypertension on.

As initiated by Pulmonology or MFM if patient or fetus in distress– Patient to be sent to EUHM E.D.

Delivery management

Optimal timing of delivery involves assessment of maternal cardiopulmonary status as well as consideration of risks of prematurity to the neonate. Table 4 describes a Hospital Checklist which can aid on admission to ensure all aspects of delivery planning have been discussed and planned. Delivery should be considered if there is evidence of maternal decompensation. In patients who remain stable, delivery is recommended between 34-36 weeks gestation as continuation of pregnancy beyond this point has been associated with higher incidence of maternal decline [7]. Preterm delivery is a common outcome associated with pulmonary hypertension in pregnancy with only 15-25% of pregnancies progressing to term [15]. Most deliveries are indicated based on maternal cardiopulmonary status. Gestational age at delivery appears to be correlated with severity of pulmonary

hypertension with patients with more severe forms of pulmonary hypertension delivering at earlier gestational ages [8].

Table 2: Recommendations for antenatal care in patients with PAH

1st trimester

- ☐ Ultrasound for dating
- ☐ Offer genetic screening
- ☐ Referral to tertiary care center with an experienced pulmonary hypertension program
- ☐ Maternal-fetal medicine consultation with counseling regarding pregnancy options including pregnancy termination
- ☐ Echocardiogram
- ☐ Identify members of multidisciplinary team and outline plan of care should patient present and require admission
- ☐ Identify patient's health care proxy in the event of emergency

2nd trimester

- ☐ Detailed fetal anatomic survey
- ☐ If PAH associated with maternal congenital heart defect or other risk factors, consider fetal echocardiogram
- ☐ Continued close follow-up with pulmonary hypertension team and maternal-fetal medicine
- ☐ Repeat echocardiograms
- ☐ Serial growth ultrasounds starting at 24- weeks of gestation
- ☐ Begin counseling and planning regarding postpartum contraception
- ☐ Consider neonatology consultation
- ☐ Multidisciplinary team meetings to review patient status and plan of care should patient require admission or urgent delivery

3rd trimester

- ☐ Continue serial growth ultrasounds
- ☐ Consider antenatal testing starting at 32 weeks
- ☐ Continue close follow-up with pulmonary hypertension team and maternal fetal medicine
- ☐ Repeat echocardiograms
- ☐ Anesthesia consultation for delivery planning
- ☐ Multidisciplinary team meeting to decide timing and mode of delivery
- ☐ Administer course of betamethasone for fetal lung maturity if delivery planned prior to 37 weeks

Mode of delivery should be carefully considered in patients with pulmonary hypertension. Vaginal delivery carries several risks. Valsalva in the setting of pulmonary hypertension increases intrathoracic pressure which thus decreases venous return and preload and can lead to cardiopulmonary collapse. A similar decrease in preload can be seen with labor-induced vasovagal re-

sponses. Sympathetic response to pain can also lead to decompensation. Vasopressors or inotropic support may be required during labor to help compensate for these changes. Effective analgesia is critical if vaginal delivery is considered in the setting of pulmonary hypertension and therefore early epidural placement is recommended. Assisted-second stage of labor with the use of vacuum or forceps to avoid maternal pushing should also be considered. Elective cesarean section avoids these potential complications of labor and allows for a multidisciplinary planning approach to delivery. Patients with WHO Group 1 pulmonary hypertension and those with severely elevated mean pulmonary arterial pressures have a high risk of decompensating during delivery and thus cesarean section is the preferred mode of delivery for these patients [7]. The mortality rate for women with pulmonary hypertension who undergo a successful trial of labor is 5% while planned cesarean delivery is associated with a 9% mortality rate. However, in those who required intrapartum cesarean delivery following an unsuccessful trial of labor mortality was as high as 33% [9]. These data highlight the importance of careful patient selection when considering a trial of labor in this patient population.

Patients should have close monitoring during delivery regardless of mode. There is no consensus regarding the use of pulmonary artery catheterization during delivery. However, Swan-Ganz catheter placement may be useful in some cases. A multi-disciplinary approach to delivery which includes obstetricians, maternal fetal medicine specialists, anesthesiologists (both cardiac and obstetric), pulmonary hypertension specialists, and cardiothoracic surgery is recommended. In select patients, cesarean section in an operating room equipped for transition to ECMO with arterial and venous access obtained prior to surgery may be considered.

Oxytocin should be used with caution in patients with pulmonary hypertension as it is known to be a systemic vasodilator. Its use has been associated with decreased systemic vascular resistance, increased pulmonary vascular resistance, and a drop in cardiac output. Postpartum oxytocin should be titrated according to heart rate and blood pressure.

Anesthesia considerations

Both neuraxial and general anesthesia have been successfully used in patients with pulmonary hypertension.

Table 3: Team for management of pregnant patients with pulmonary arterial hypertension.

Physicians	Nursing	Other
<ul style="list-style-type: none"> □ Obstetrician □ Maternal-fetal medicine □ Pulmonary hypertension specialist □ Anesthesiology □ Neonatologist □ Cardiothoracic surgeon 	<ul style="list-style-type: none"> □ OB Nursing □ OB surgical tech □ Pulmonary hypertension nursing □ ICU nursing □ Neonatal nursing □ ECMO team 	<ul style="list-style-type: none"> □ Pharmacy □ OR scheduling □ Respiratory therapy

Table 4: Hospital admission checklist for pregnant patients with PAH.

-
- o Communicate with defined PAH team members: communication tree activated by Ob/MFM or pulmonary critical care
 - o Arterial line, peripheral IV, and other access as needed
 - o Assess presence of fetal heart tones if prior to viability.
 - o Consents signed for Cesarean section, tubal ligation (if applicable), and blood transfusion
 - o Evaluation by pulmonary hypertension team
 - o OB anesthesia and cardiac anesthesia consultation
 - o Consider CT surgery consultation if possibility of ECMO is anticipated
 - o Administer betamethasone for fetal lung maturity if after viability
 - o Obtain and confirm back up epoprostenol pump and cassette in OR at the time of delivery if applicable
 - o Coordinate NICU equipment availability in OR with OB nursing and NICU team
 - o Avoid emergent delivery; discuss with patient plans if non-reassuring fetal status
 - o C-section tray to bedside in the event of maternal code requiring delivery to facilitate resuscitation
 - o Review signs and symptoms of postpartum hemorrhage with intensive care nursing team
 - o Uterotonics (misoprostol) and Bakri balloon at bedside
-

In general, neuraxial anesthesia is preferred given concerns with increased pulmonary arterial pressure during laryngoscopy and tracheal intubation as well as concerns for adverse effects of positive-pressure ventilation on right ventricular after load and ultimately cardiac output. The main focus should be on avoiding increases in pulmonary vascular resistance while maintaining right heart contractility.

Epidural placement with slow, incremental dosing has been the most successful approach in these patients. Low-dose combined spinal-epidural analgesia may also be considered. This method may provide a denser perineal block than epidural alone. Single-dose spinal should be avoided in this patient population due to risk of rise of the block and thus rapid development of hemodynamic instability.

Anesthetic agents known to be associated with less vasodilation and cardiac depression such as midazolam and fentanyl are recommended. Vasopressors and inotropes should be used as needed to maintain mean arterial pressures. Fluid therapy should be guided by overall clinical status and continuous assessment of vital signs with care to avoid excessive right heart filling pressures.

Postpartum care

The postpartum period with its associated fluid shifts is a critical period for these patients. In a study of 49 cases of pulmonary hypertension in pregnancy, 8 maternal deaths were noted, all of which occurred during the postpartum period [9]. Careful monitoring of symptoms and titration of medications as needed is recommended. Due to the risk of mortality and need for tight titration of epoprostenol, we recommend ICU admission postpartum. Most women will require diuretics in the postpartum period to assist in the management of fluid shifts. Standard DVT prophylaxis during the postpartum period is also recommended.

Neonatal outcomes

Neonatal outcomes in patients with pulmonary hypertension are largely dictated by the degree of prematurity. Overall survival rates are 87-89% with the main risk to the fetus being maternal hypoxia. There is a ~70% rate of preterm delivery in patients with pulmonary hypertension with a median gestational age of 35 weeks. Approximately 24% of neonates in a review of cases were noted to be small for gestational age at birth [9]. All of our patients were delivered prematurely but given their PAH required epoprostenol these were all serious cases of PAH. *Cur Op Gyn Obs*, 2(1):346-353 (2019)

Conclusion

Prompt diagnosis and initiation of treatment for pulmonary hypertension in pregnancy, along with a multidisciplinary approach to care are crucial to improved maternal and neonatal outcomes. Patients presenting in pregnancy should be counseled regarding risks and offered termination given the high mortality rate. Close follow-up with the care team during pregnancy is recommended with hospitalization and consideration of delivery should signs of maternal right heart failure refractory to outpatient therapy develop. Given chronic maternal hypoxia associated with placental hypoperfusion, fetal growth should be followed closely. Mode of delivery should be tailored to the patient, but in general mortality risk is lower with successful trial of labor or planned cesarean section. Incremental-dosed epidural is the preferred mode of analgesia in patients with pulmonary hypertension due to limited effects of overall hemodynamic status. Timing of delivery is also dictated by maternal cardiopulmonary status but is recommended between 34-36 weeks gestation in stable patients. Patients should be monitored closely during the postpartum period for signs of developing right heart failure due to fluid shifts. Neonatal outcomes depend largely on the degree of prematurity. In general, care should be individualized to the patient given severity of disease in combination with long-term goals.

Early establishment of a multidisciplinary team is important to successful pregnancy management. We outline a plan for care in women with significant PAH requiring epoprostenol. We included a list of multidisciplinary care team members, communication tree in case of unplanned admission, antenatal care outlined per trimester and a delivery hospitalization checklist to aid in the care of these complex patients.

Conflict of interest

The authors declare no conflict of interest.

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