

## Treatment of pulmonary arterial hypertension in pregnancy

SHEILYN HUANG AND EVELYN R. HERMES DESANTIS

**P**ulmonary arterial hypertension (PAH) is a disease characterized by narrowing of the pulmonary arteries and increased vascular resistance. Some of the key factors that contribute to vascular resistance include vasoconstriction, thrombosis, and vascular proliferation and remodeling. PAH can be characterized as idiopathic or familial or associated with collagen vascular disease, congenital heart disease, portal hypertension, HIV infection, the use of certain drugs, or thyroid disorders.<sup>1</sup> Hemodynamically, PAH is defined as a systolic pulmonary arterial pressure of >30 mm Hg or a mean pulmonary arterial pressure of >20 mm Hg.<sup>2</sup> The increased blood pressure in the pulmonary vessels eventually leads to right ventricular hypertrophy and failure. Women with PAH should avoid becoming pregnant, as the physiological, cardiovascular, and pulmonary changes that occur during pregnancy can exacerbate the condition.<sup>3</sup> During pregnancy, blood volume and cardiac output increase by 40%, and uterine contractions during labor contribute to additional hemodynamic changes. After delivery, cardiac output and systemic vas-

**Purpose.** The treatment of pulmonary arterial hypertension (PAH) in pregnancy is reviewed.

**Summary.** PAH is a disease characterized by narrowing of the pulmonary arteries and increased vascular resistance. Women with PAH should avoid becoming pregnant, as the physiological, cardiovascular, and pulmonary changes that occur during pregnancy can exacerbate the condition. However, several viable treatment options are available to improve the outcomes in this patient population, including inhaled nitric oxide, calcium-channel blockers, targeted pulmonary vasodilators, and sildenafil. Epoprostenol, a naturally occurring prostaglandin and vasodilator, is a pregnancy category B drug. Reproductive studies in rats and rabbits have found no impaired fertility or fetal harm at 2.5–4.8 times the recommended human dosage of epoprostenol. Most of the published case reports describe initiating epoprostenol 2–4 ng/kg/min i.v. several weeks before or near the time of delivery. Iloprost is a pregnancy category C drug but has demonstrated benefit in pregnant pa-

tients with PAH, with no congenital abnormalities and no postpartum maternal or infant mortality reported. Sildenafil causes vasodilation of the pulmonary vascular bed and vasodilation in the systemic circulation. Two case reports have described the successful treatment with sildenafil, a pregnancy category B drug, of pregnant patients with PAH. Patients with idiopathic PAH or chronic thromboembolic PAH should receive full-dose subcutaneous low-molecular-weight heparin therapy instead of warfarin for bleeding prophylaxis during pregnancy.

**Conclusion.** Targeted pulmonary vasodilators are viable treatment options for pregnant patients with PAH. Early recognition and management of worsening symptoms are essential to improve outcomes for both the mother and infant.

**Index terms:** Anticoagulants; Calcium antagonists; Dosage; Epoprostenol; Heparins; Hypertension; Iloprost; Nitric oxide; Pregnancy; Sildenafil; Site of action; Toxicity; Vasodilating agents; Warfarin

**Am J Health-Syst Pharm.** 2007; 64:1922-6

cular resistance increase significantly due to an autotransfusion of approximately 500 mL from the utero-placental unit.<sup>4</sup> It may take up to six months for the hemodynamic values

to return to prepregnancy levels, but most of the changes occur during the first two weeks after delivery. The maternal mortality rates during pregnancy are 30% for patients with

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primary pulmonary hypertension, 36% for women with Eisenmenger's syndrome, and 50% for patients with secondary vascular hypertension.<sup>5</sup> Maternal death usually occurs during the third trimester, with the highest risk of death occurring during the first 10 days after delivery.<sup>6</sup> In addition, premature delivery occurs in over 50% of pregnancies in women with PAH; only 15–25% of pregnancies reach full term.<sup>7</sup> The survival rate of neonates delivered by mothers with PAH is 87–89%. The main risk to the fetus is associated with maternal hypoxia, which can lead to growth retardation, premature delivery, and stillbirth.<sup>3</sup> If PAH is detected early in pregnancy, patients may be counseled to consider termination of the pregnancy.

Several viable treatment options are available to improve the outcomes in this patient population, including inhaled nitric oxide (a generalized vasodilator used in the antepartum period),<sup>8</sup> calcium-channel blockers,<sup>9</sup> targeted pulmonary vasodilator therapy (epoprostenol, iloprost), and sildenafil (Figure 1). This review focuses on the treatment of PAH in pregnancy with targeted pulmonary vasodilators.

### Treatment options

To date, there have been no large, single-center studies involving PAH during pregnancy; however, relevant case reports have been published in the medical literature.

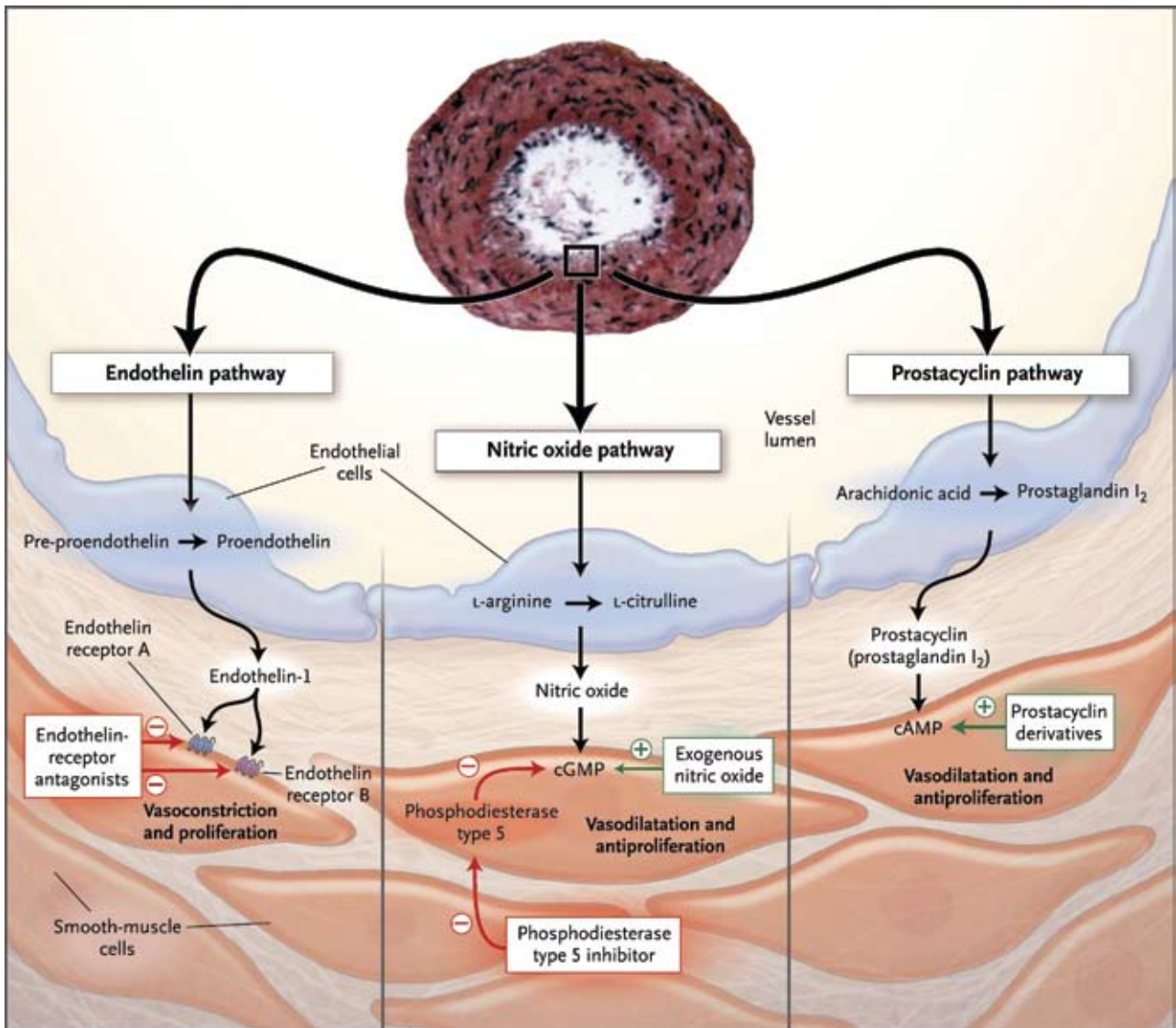
**Prostacyclin analogues.** Epoprostenol, a naturally occurring prostaglandin and vasodilator, is a

pregnancy category B drug.<sup>6</sup> Reproductive studies in rats and rabbits have found no impaired fertility or fetal harm at 2.5–4.8 times the recommended human dosage of epoprostenol.<sup>10</sup> At least 12 case reports have described the use of i.v. epoprostenol in pregnant patients with PAH, including those with severe disease.<sup>4,7,11–16</sup> In these case reports, epoprostenol was initiated for most patients several weeks before or near the time of delivery<sup>4,7,11,13–16</sup>; four patients began receiving continuous i.v. infusions of epoprostenol before pregnancy.<sup>7,12,16</sup> The initial dosage of epoprostenol is usually 2–4 ng/kg/min i.v. and is adjusted accordingly. In one case, i.v. epoprostenol was initiated at 23 weeks of gestation when the patient began experiencing increasing dyspnea.<sup>7</sup> The dosage was increased to 20 ng/kg/min. The patient had a cesarean section at 32 weeks and delivered a 1.7-kg girl with Apgar scores of 9 at one minute and 10 at five minutes. The patient was discharged on epoprostenol therapy, and both mother and baby were doing well at one year postpartum.<sup>7</sup> Another patient received epoprostenol through a Hickman catheter for one year before becoming pregnant.<sup>7</sup> At 7 weeks' gestation, her epoprostenol dosage was increased to 12 ng/kg/min. She underwent an uneventful cesarean section at 32 weeks and delivered a 1.53-kg male infant with normal Apgar scores. Another patient with New York Heart Association (NYHA) functional class IV PAH became severely dyspneic at 26 weeks' gestation.<sup>4</sup> She was initiated on epoprostenol 4 ng/kg/min i.v., which was increased to 11.8 ng/kg/min. Due to concerns about epoprostenol-related platelet inhibition during epidural catheter placement and labor, her therapy was switched to inhaled epoprostenol, under a Food and Drug Administration-approved investigational new drug license, before delivery. A 2.25-kg male infant with Apgar scores of 7 and 9 at one

and five minutes, respectively, was delivered vaginally at 35 weeks. The patient was restarted on i.v. epoprostenol after delivery and was discharged to her home. Both mother and baby were well at six months' follow-up. The use of epoprostenol did not result in any fetal deformities or growth retardation in any of these children, all of whom were alive and healthy at delivery and follow-up. The deaths of two mothers treated with epoprostenol have been reported. One patient was reported to have experienced increasing shortness of breath, fatigue, and edema for several weeks during her pregnancy before PAH was diagnosed.<sup>16</sup> On admission, she had severe right ventricular failure and was treated immediately with epoprostenol. Despite therapy, she died eight hours after the diagnosis of PAH. In another case, the patient did not receive nebulized iloprost until after a cesarean section.<sup>11</sup> I.V. epoprostenol was also initiated. Her symptoms continued to deteriorate, and she died 14 days postpartum. These two cases demonstrate the need for early recognition and management of worsening symptoms of PAH in order to improve outcomes.

Iloprost is a prostacyclin analogue that can reduce vascular resistance and arterial pressure. Five cases of pregnant patients who received nebulized iloprost for PAH have been published.<sup>6,17</sup> Although iloprost is a pregnancy category C drug,<sup>18</sup> all infants were free from congenital abnormalities and there was no postpartum maternal or infant mortality. One patient had NYHA functional class II PAH and was stabilized on bosentan therapy.<sup>17</sup> Since bosentan is a pregnancy category X drug, it was discontinued at 8 weeks of gestation, and nebulized iloprost was initiated. At 24 weeks of gestation, the patient developed increasing dyspnea, and the dosage of nebulized iloprost was increased to 20 µg eight or nine times daily. At 25 weeks' gestation, the patient suffered cardiorespira-

**Figure 1.** Three major pathways involved in abnormal proliferation and contraction of pulmonary artery (PA) smooth-muscle cells in patients with pulmonary arterial hypertension (PAH) are shown. A transverse section of a small PA (<500 μm in diameter) from a patient with severe PAH (top) shows intimal proliferation and marked medial hypertrophy. Dysfunctional PA endothelial cells (blue) have decreased production of prostacyclin and nitric oxide and increased production of endothelin-1—a condition promoting vasoconstriction and proliferation of smooth-muscle cells in the PA (red). Current or emerging therapies interfere with specific targets in smooth-muscle cells in the PAs. In addition to their actions on smooth-muscle cells, prostacyclin derivatives and nitric oxide have several other properties, including antiplatelet effects. Plus signs denote an increase in intracellular concentration. Minus signs denote blockade of a receptor, inhibition of an enzyme, or a decrease in intracellular concentration. cAMP = cyclic adenosine monophosphate, cGMP = cyclic guanosine monophosphate. Figure reproduced and caption adapted, with permission, from reference 1.



tory arrest; however, she was resuscitated and switched to i.v. iloprost (not available in the United States). Five days later, a cesarean section was performed and a 0.65-kg male infant was delivered. The infant's Apgar scores were 8 at one minute and 9 at five minutes. One month

postpartum, the patient discontinued the iloprost and was restarted on bosentan. Both mother and son were doing well at the 16-month follow-up visit. Another patient with NYHA functional class II or III PAH received nebulized iloprost at 19 weeks' gestation. The dosage was increased to

10 μg seven times daily. The patient underwent a cesarean section at 36 weeks and delivered a 2.8-kg male infant with an Apgar score of 9 at 1 and five minutes. Nebulized iloprost was discontinued 1 month postpartum, with the patient stable in NYHA functional class II. Both mother and

son remained well 18 months later. Another case report described the use of nebulized iloprost in a patient with NYHA functional class II or III PAH.<sup>17</sup> The patient became increasingly symptomatic at 17 weeks' gestation, so nebulized iloprost was initiated. The dosage was increased to 15 µg seven times daily. A cesarean section was performed at 35 weeks, and a 2.16-kg female infant was delivered. The Apgar scores were 9 at 1 minute and 10 at 5 and 10 minutes. The infant progressed well, and the mother was stable in NYHA functional class II at 12 weeks postpartum. A fourth patient had stable PAH up to week 26 of gestation.<sup>6</sup> Nebulized iloprost in dosages of 15 µg was initiated during week 28 and resulted in decreased pulmonary arterial pressure. A cesarean section was performed at 28 weeks, and a 1.1-kg female infant was delivered. The baby's Apgar score was 9 at 1 and 5 minutes. The mother continued nebulized iloprost 20 µg every four hours for 16 days, which was eventually discontinued. Both mother and daughter were well at 18 months' follow-up. The fifth patient was treated with iloprost in addition to epoprostenol in the postpartum period. Details of her case were described earlier.<sup>11</sup>

**Phosphodiesterase type-5 inhibitors.** Sildenafil causes vasodilation of the pulmonary vascular bed and vasodilation in the systemic circulation. Two case reports have described the successful treatment with sildenafil of pregnant patients with PAH.<sup>19,20</sup> Sildenafil is a pregnancy category B drug. In the first case, the patient was stabilized on sildenafil 50 mg p.o. and sublingual nifedipine 20 mg before becoming pregnant.<sup>19</sup> After 7 weeks of amenorrhea and a positive pregnancy test, sildenafil 150 mg daily p.o. and diltiazem 60 mg daily p.o. were initiated. At 9 weeks of gestation, sildenafil was discontinued due to financial reasons, and the diltiazem dosage was increased to 180 mg daily p.o. During this time

period, the patient progressed from NYHA functional class II to class IV. At 31 weeks of gestation, sildenafil 150 mg daily p.o. was reintroduced and diltiazem was discontinued. The patient did not show any clinical improvement 1 week later, so L-arginine 3 g daily p.o. was added. The patient improved to NYHA functional class III four days later. A cesarean delivery was scheduled at 36 weeks of gestation. Sildenafil and L-arginine were discontinued overnight before the cesarean section, and the patient remained asymptomatic during delivery. A male infant weighing 2.29 kg with Apgar scores of 9 at one and five minutes was delivered. Postdelivery, sildenafil 150 mg daily p.o. was restarted in combination with L-arginine 6 g daily p.o. The patient was discharged on sildenafil 150 mg daily p.o., L-arginine 6 g daily p.o., and diltiazem 180 mg daily p.o. after seven days. The second case report involved a patient with NYHA functional class III PAH who was stabilized on bosentan for nine months before her pregnancy.<sup>20</sup> During the pregnancy, she was treated with sildenafil and bosentan. The patient delivered a healthy, 1.41-kg female infant at 30 weeks. She continued on sildenafil and bosentan therapy postpartum.

#### Preventing thromboembolic events

Patients with idiopathic PAH or chronic thromboembolic PAH are also at risk of thrombosis and thromboembolism. These patients generally receive warfarin for prophylaxis; however, warfarin is contraindicated during pregnancy. Badalian et al.<sup>12</sup> presented the case of a patient who was receiving treatment with warfarin and epoprostenol and discovered she was pregnant with twins at 15 weeks of gestation. Two weeks later, one of the twins died. At 34 weeks' gestation, the other twin was delivered via cesarean with severe hydrocephalus and facial anomalies consistent with warfarin exposure. Therefore, full-

dose subcutaneous low-molecular-weight heparin (LMWH) therapy should be substituted for warfarin during pregnancy. Patients who experience adverse effects or bleeding may be switched from a full dosage to a prophylactic dosage. Warfarin can then be initiated in the postpartum period.<sup>17</sup> Antepartum anticoagulation is debated in patients with PAH of other etiologies, such as Eisenmenger's syndrome and systemic lupus erythematosus. Nevertheless, anticoagulation is strongly recommended in the postpartum period, regardless of PAH etiology, since deep venous thrombosis and pulmonary embolism are likely causes of postpartum mortality.<sup>3,13</sup>

#### Recommendations

Although the treatment of PAH in pregnancy is not well documented, case reports, which provide a low level of evidence, have described the successful use of targeted pulmonary vasodilator therapy in this patient population. Most of the patients were treated with i.v. epoprostenol. Sildenafil and nebulized iloprost have also been used with positive outcomes; however, evidence of their use is more limited. Epoprostenol has demonstrated a benefit in pregnant patients with NYHA functional class IV PAH. I.V. epoprostenol may be preferable for patients with severe PAH; however, i.v. epoprostenol may inhibit platelet aggregation, so patients should be monitored for bleeding, particularly during delivery and postpartum. Epoprostenol's inhibition of platelet aggregation is only temporary, lasting 20–30 minutes.<sup>4</sup> Therefore, LMWH therapy should continue, particularly if the patient has a high risk of thrombosis. Although nebulized iloprost is a pregnancy category C drug and there are conflicting reports of anomalies occurring in the offspring of rats and rabbits,<sup>18</sup> no fetal deformities were reported in the four cases described. Nebulized iloprost may be another

option for patients with more stable PAH. The optimal timing for initiating vasodilator therapy remains unclear. Deterioration of PAH generally occurs during weeks 20–24 of gestation, when most pregnancy-related hemodynamic changes occur.<sup>3</sup> If a patient's condition begins to deteriorate, vasodilator therapy should be started immediately. In cases where therapy was delayed, the outcomes were poor.<sup>11,16</sup> The risk of maternal death is highest in the days following delivery, and most of the hemodynamic values return to prepregnancy levels during the first two weeks after delivery.<sup>3</sup> For this reason, it is recommended that targeted pulmonary vasodilator therapy continue into the postpartum period until the patient is stable. Management of pregnant patients with pulmonary hypertension requires a multidisciplinary team approach with careful monitoring.

### Conclusion

Targeted pulmonary vasodilators are viable treatment options for pregnant patients with PAH. Early recognition and management of worsening symptoms are essential to improve outcomes for both the mother and infant.

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