Pulmonary Hypertension in Pregnancy: Treatment With Pulmonary Vasodilators

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Objective: **To describe the clinical course of pregnancies complicated by pulmonary hypertension and treated with the pulmonary vasodilators nifedipine and prostacyclin.**

Methods: **Four pregnant women with pulmonary hypertension were treated with pulmonary vasodilators. Therapy with oral nifedipine and intravenous prostacyclin was guided by right pulmonary artery catheterization and Doppler measurements of cardiac output.**

Results: **Three of four women responded to vasodilator therapy and successfully completed their pregnancies. Two who conceived at least 1 year after successful treatment and normalized right ventricle function carried three uncomplicated pregnancies. The woman who did not respond died. Delay in diagnosis contributed to her outcome. Noninvasive measurement of cardiac output helped diagnosis of right ventricular failure and offered reassurance in women who remained compensated. Postpartum decompensation in one woman was characterized by a negative Starling response as central venous pressure increased from 4 to 11 mmHg. She responded positively to diuresis.**

Conclusion: **Early diagnosis of pulmonary hypertension is critical. Volume overload postpartum might significantly contribute to decompensation. We recommend a year of successful therapy after a response to vasodilator therapy and near-normal right ventricular function before pregnancy is considered. In complicated pregnancies, women must balance the best estimate of risk with the value they put on pregnancy. (Obstet Gynecol 1999;93:494–8. © 1999 by The American College of Obstetricians and Gynecologists.)**

The incidence of primary pulmonary hypertension is one to two per million.[1] Women are affected four to five times more often than men. Familial (autosomal dominant) primary pulmonary hypertension accounts for 6% of all cases and expresses a pattern of genetic anticipation. Secondary pulmonary hypertension can develop as a complication of cardiac and pulmonary disease or as a complication of drugs such as cocaine or appetite suppressants.[1] If pulmonary hypertension is untreated, the median survival after diagnosis is 2.5 years.[2] Of the minority of patients who initially respond to nifedipine, 5-year survival rate is 95%.[3] The 5-year survival rate of those who require treatment with prostacyclin is 54%.[4] The beneficial hemodynamic effects of prostacyclin infusion can be sustained for longer than 1 year.[5]

Maternal mortality rate from severe pulmonary hypertension was reported as high as 50%.[6–8] Sudden, irreversible deterioration in the postpartum period is common.[6,7,9] A single case of short-term treatment of pulmonary hypertension with nifedipine in pregnancy was reported.[10] The prognosis for pregnancy in women who had good responses to vasodilator therapy is unknown. The goal of the present study was to review our experience with pulmonary vasodilation and develop recommendations for the treatment and counseling of women with pulmonary hypertension.

Materials and Methods

We retrospectively assessed pregnant women with pulmonary hypertension. Subjects included were pregnant women with pulmonary hypertension, without evidence of intracardiac shunt, with systolic pulmonary pressure exceeding 60 mmHg, with evidence of right ventricular dysfunction, and who were treated with nifedipine or prostacyclin. Patients were evaluated with echocardiography, pulmonary arterial catheterization, and Doppler measurement of cardiac output.[11,12] Laboratory assessment was directed by clinical management teams. Data were gathered from clinic charts.

Results

Four women with pulmonary hypertension carried a total of five pregnancies. At the time of diagnosis, each had severe, life-threatening pulmonary hypertension with systolic pulmonary pressures exceeding 70 mmHg

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PII S0029-7844(98)00524-9

Table 1. Characteristics of Patients With Pulmonary Hypertension

Patient	Age (y)	Parity	Duration of symptoms (mo)	Symptoms	Diagnosis
1	25	0	4	Dyspnea, dry cough, swelling	28 weeks*
2	35	1	3	Dyspnea, dry cough, fatigue, hoarseness, swelling	27 weeks*
3	30	0	6	Near syncope	15 months†
4	26	1	5	Dyspnea, fatigue, syncope	12 months†

* Weeks of pregnancy.
† Months before pregnancy.

and right ventricular dilatation and dysfunction. Each woman was treated with the pulmonary vasodilators nifedipine, prostacyclin, or both. Pregnancy outcomes varied depending on response to therapy and interval between diagnosis and treatment, and on the pregnancy itself.

Clinical presentations are given in Table 1. In two women, pulmonary hypertension was diagnosed during pregnancy, and in two, a year or more before conception. Each had nonspecific symptoms for months before diagnosis. Table 2 gives the results of pertinent diagnostic tests. Pulmonary artery pressures and pulmonary vascular resistance were increased; cardiac output was reduced. Echocardiography was used to assess that right ventricular function was severely impaired.

Table 3 describes patient management. Patient 1 had severe right ventricular failure, with cardiac output of 2.0 L/minute and severe metabolic acidosis on admission. Despite treatment with dobutamine, prostacyclin, and HCO_3 replacement, she died 8 hours after diagnosis. The family wished that neither a postmortem cesarean nor an autopsy be done.

Patients 2, 3, and 4 had initial responses to therapy with decreased pulmonary vascular resistance and increased cardiac output. Patient 2 responded to nifedipine with cardiac output increased to 7.1 L/minute; however, despite increasing doses, cardiac output measured by Doppler[11–13] decreased to 5.8 L/minute and subsequently to 4.5 L/minute despite increasing doses of nifedipine (Figure 1). Symptoms, edema, and pulmonary pressures measured by echocardiography remained unchanged. Subsequent treatment with prostacyclin directed by pulmonary artery catheter improved cardiac output and pulmonary vascular resistance.

Table 4 describes management of labor and delivery, outcomes of pregnancy, and maternal condition postpartum. During labor and delivery, we maintained hemodynamic stability, pain control, and adequate oxygenation. Two of four deliveries were managed with pulmonary arterial catheters. Regional anesthesia was used in each delivery and delivery modes were based on obstetric indications.

In patients 3 and 4, pulmonary hypertension was diagnosed and treated successfully a year or more before conception. Patient 3 was counseled on the risks of pregnancy 5 months after diagnosis. She was asymptomatic with cardiac output of 6.2 L/minute. Pulmonary hypertension of the severity of hers at diagnosis has been associated with a maternal mortality rate as high as 50%. Because she responded to nifedipine, her risks were probably lower but could not be quantified accurately. We encouraged her to delay pregnancy for 6 to 9 more months to confirm the longevity of her response. Seven months later, she was asymptomatic, tolerating heavy exercise, and maintaining normal right ventricular function, so she decided to attempt pregnancy.

Table 2. Condition at Diagnosis

Patient	PAP (mmHg)	Cardiac output (L/min)	PVR (dyne · sec · cm^{-5})	V/Q scan	SGOT	HCO_3	Echocardiographic findings
1*	75/40	2.0	1710	Low probability	Increased	4	Severe right ventricular dilatation, interventricular septal wall collapse
2*	78/32	4.5	637	Low probability	Increased	13	Severe right ventricular dilatation, paradoxical septal wall motion
3†	74/30	4.8	728	Low probability			Severe right ventricle dilatation, paradoxical septal wall motion
4†	110/46	4.4	1024	Low probability	Normal	23	Severe right dilatation, paradoxical septal wall motion

PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; V/Q scan = ventilation/perfusion scan; SGOT = serum glutamic-oxalic transaminase; HCO_3 = bicarbonate.
* During pregnancy.
† Before pregnancy.

Table 3. Treatment Variables

Patient	Pulmonary vasodilator	Response: PVR (dyne · sec · cm^{-5})	Response: CO (L/min)	Response: PAP (mmHg)	Response: Clinical	Anticoagulation	Oxygen
1*	IV prostacyclin	None	None	None	None	Heparin	Yes
2*	Nifedipine 120 mg	451	5.5	60/28	Diurese 9 kg	Heparin	Yes
	IV prostacyclin	756–684	3.5–5.6	72/30			
3†	Nifedipine 90 mg	290	6.1–7.0	38/14	Normal‡ right ventricle	Coumadin to heparin	No
4†	IV prostacyclin	221	5.0–6.0	45/25	Normal‡ right ventricle	Coumadin to heparin	No

PVR = pulmonary vascular resistance; CO = cardiac output; PAP = pulmonary artery pressure; IV = intravenous.
* During pregnancy.
† Before pregnancy.
‡ For 1 year or more.

Patient 4 presented at 11 weeks' gestation with an unexpected pregnancy. She was also counseled about her uncertain prognosis in pregnancy. Although prostacyclin was not expected to have adverse effects in pregnancy, we could find no published studies to validate its safety. She was counseled on the risks of coumadin embryopathy, and we changed her prescription to subcutaneous heparin. She elected to continue the pregnancy.

Patients 3 and 4 had normalized pulmonary artery pressures and recovered right ventricle function before pregnancy. They carried their pregnancies without major complications. Patient 3 completed a second pregnancy without complications 1 year after the first. Patient 4 was converted successfully from prostacyclin to nifedipine 8 weeks postpartum and remained well compensated 1 year after conversion.

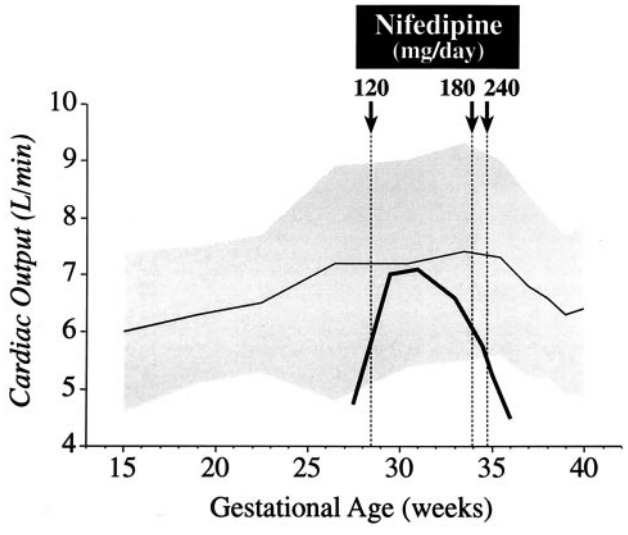

Figure 1. Cardiac output of Subject 2 during gestation, showing initial response to nifedipine and the subsequent failure to respond (*thick line*). The solid line represents mean cardiac output (*thin line*), the shaded area represents one standard deviation.[13]

Patient 2 had a complicated postpartum course. On the third postpartum day, her hematocrit level fell to 25%, she was transfused with 2 units of packed cells, and became progressively short of breath. Central venous pressure increased from 4 to 11 mmHg, and her weight increased 2 kg. Cardiac output decreased from 6.8 to 2.5 L/minute with an increase in pulmonary vascular resistance from 447 to 1256 dyne · sec · cm^{-5}. Systemic pressure was supported with dopamine, prostacyclin dose was increased, and we believed she might die.

Figure 2 shows the patient's Starling curve during the 24 hours of deterioration and recovery. As her central venous pressure increased from 4 to 11 mmHg, her cardiac output did not increase but decreased precipitously from 6 to 2.5 L/minute. The acute volume load might have further dilated the right ventricle, increasing displacement of the intraventricular septum into the left ventricle, compromising left ventricular filling, and decreasing stroke volume.[14] Her right ventricle was functioning entirely on the failure side of the Starling curve; therefore, she was carefully diuresed. Over 24 hours she lost 2 kg of weight. Central venous pressure decreased to 2 mmHg, cardiac output increased to 6.1 L/minute, and pulmonary vascular resistance decreased to 509 dyne · sec · cm^{-5}. Her hemodynamic findings stabilized over the next 2 weeks.

Discussion

Patient 1 showed the malignant potential of pulmonary hypertension in pregnancy. Diagnosis was preceded by weeks of increasing tiredness, shortness of breath, and edema, symptoms ubiquitous in pregnancy. When pulmonary hypertension was diagnosed, she was hypoxic and acidotic from poor tissue perfusion. Her right ventricle was in failure from excessive afterload and volume load associated with advancing pregnancy. Her acidosis and hypoxemia promoted pulmonary hyper-

Table 4. Pregnancy Outcomes

Patient	Gestational (wk)	Delivery	PA catheter	Anesthesia	Birth weight (g)	Condition
1	28	None	Yes			Died
2	36	Vaginal	Yes	Narcotic/Epidural	3333	NYHA IV transplant list
3	39	Vaginal	No	Epidural/Caudal	2772	NYHA I
	38	Vaginal	No	Epidural	3232	NYHA I
4	39	Vaginal	Yes	Epidural/Caudal	2905	NYHA I to nifedipine

PA = pulmonary artery; NYHA = New York Heart Association class.

tension; her right ventricle was volume overloaded, but she could not tolerate diuresis. Despite use of prostacyclin, she could not be saved. Any discussion of pregnancy in patients with pulmonary hypertension should be placed in the context of that daunting clinical scenario.

Patients 2, 3, and 4 showed the effects of improved diagnostic and therapeutic modalities. Patient 2 presented similarly to patient 1, but her hypertension was diagnosed earlier in her clinical course. The insidious nature of her worsening symptoms delayed diagnosis. She had volume overload and right ventricle failure. She was hypoxic but only mildly acidotic (HCO_3 was 13 mEq/L). Her initial response to pulmonary vasodilation with nifedipine improved systemic perfusion and initiated diuresis. During the next 4 weeks her cardiac output increased from 4.8 to 7.2 L/minute. Her subsequent deterioration and need for treatment with prostacyclin was determined by decreasing cardiac output measured noninvasively.

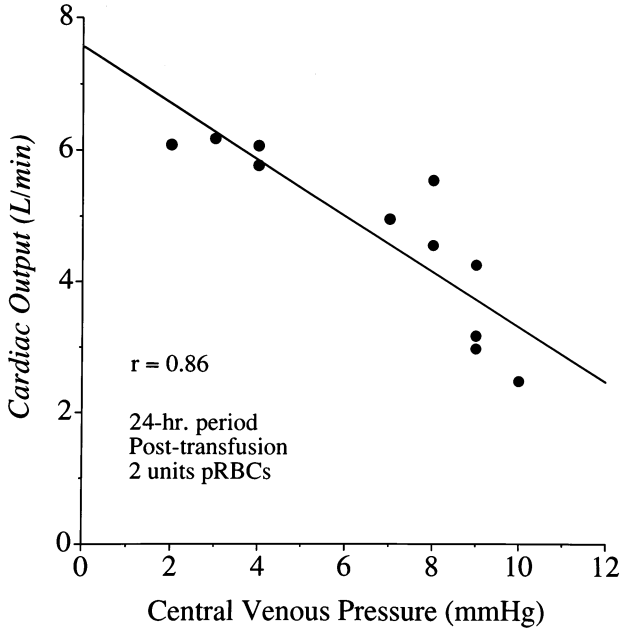

Figure 2. Cardiac output versus central venous pressure for Subject 2 during postpartum decompensation.

Patient 2 had postpartum decompensation that was well described in women with pulmonary hypertension.[6,7,9] Diuresis had a greater effect on her improvement than afterload reduction with prostacyclin. When the patient lost 2 kg, central venous pressure returned to previous levels, and cardiac output improved. Diuresis to treat systemic hypotension and worsening perfusion might not seem intuitively sound and might even seem misguided; however, we suspect that severity of right ventricular failure is frequently not appreciated. Early, careful diuresis immediately postpartum might improve the outcomes of women with pulmonary hypertension.

Patients 3 and 4 showed the potential for long-term improvement of patients treated with pulmonary vasodilators. Concurrent pregnancy at the time of diagnosis of pulmonary hypertension might have had a grave prognosis. In both cases, pulmonary artery pressures decreased significantly, and right ventricular function normalized before conception. Pregnancy was well tolerated, and right ventricular function did not deteriorate during pregnancy. From those two cases, we cannot estimate accurately the risk of undertaking pregnancy; however, given the lack of deterioration of ventricular function during pregnancy, we believe that the risk is closer to that of untreated patients with similar clinical findings than it is to women with disease comparable to theirs at diagnosis.

From these cases, we believe the following observations can be made: 1) Early diagnosis is critical. Fatigue and shortness of breath are common in pregnancy. Progressive symptoms, a cough, hoarseness, or disproportionate lower edema should reduce the threshold to test. The number of tests with negative results should exceed the number with positive results. 2) Right ventricular failure postpartum might be precipitated by

increased pulmonary vascular resistance or insidious volume overload, leading to Starling failure when cardiac output decreases as ventricular volume increases. We believe that reduction of preload postpartum might be as important as pulmonary vasodilation. 3) Noninvasive measurement of cardiac output facilitated diagnosis of recurring right ventricular failure and offered reassurance in women who remained well compensated. 4) We recommend at least a year of successful vasodilator therapy and near-normal right ventricular function before pregnancy is considered. Cardiac function and pulmonary pressures at the time of pregnancy might be better predictors than the patient's previous conditions.

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Received August 17, 1998.
Received in revised form October 22, 1998.
Accepted November 5, 1998.