Management of Pulmonary Arterial Hypertension During Pregnancy

A Retrospective, Multicenter Experience

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Background: Pulmonary arterial hypertension (PAH) is a rare disease with a predilection for young women that is associated with right ventricular failure and premature death. PAH can complicate pregnancy with hemodynamic instability or sudden death during parturition and postpartum. Our aim was to examine the impact of PAH on pregnancy outcomes in the modern era.

Methods: We conducted a retrospective evaluation of pregnant patients with PAH managed between 1999 and 2009 at five US medical centers. Patient demographics, medical therapies, hemodynamic measurements, manner of delivery, anesthetic administration, and outcomes were assessed.

Results: Among 18 patients with PAH, 12 continued pregnancy and six underwent pregnancy termination. Right ventricular systolic pressure in patients managed to parturition was 82 ± 5 mm Hg and in patients with pregnancy termination was 90 ± 16 mm Hg. Six patients underwent pregnancy termination at mean gestational age of 13 ± 1.0 weeks with no maternal deaths or complications. Twelve patients elected to continue their pregnancy and were hospitalized at 29 ± 1.4 weeks. PAH-specific therapy was administered to nine (75%) at time of delivery consisting of sildenafil, IV prostanooids, or combination therapy. All parturients underwent Cesarean section at 34 weeks with one in-hospital death and one additional death 2 months postpartum for maternal mortality of 16.7%.

Conclusions: Compared with earlier reports, maternal morbidity and mortality among pregnant women with PAH was reduced, yet maternal complications remain significant and patients should continue to be counseled to avoid pregnancy.

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Abbreviations: IRB = institutional review board; PAH = pulmonary arterial hypertension; RVSP = right ventricular systolic pressure; WHO = World Health Organization

Pulmonary arterial hypertension (PAH) is a progressive disease that preferentially affects women of childbearing age and is characterized by an elevated pulmonary vascular resistance often leading to right

ventricular failure and death if untreated.^{1,2} Historically, parturients with PAH have been described to experience adverse outcomes as the added physiologic demands of pregnancy and parturition can precipitate right ventricular failure leading to maternal and/or fetal complications. In an early report of maternal

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outcomes associated with pulmonary hypertension in pregnancy, nine of 16 patients (56%) died during or shortly after childbirth.³ Other case series described episodes of sudden hemodynamic instability associated with maternal and fetal mortality rates of 11% to 50%.^{4,5} Consequently, expert consensus guidelines strongly recommend that women with PAH, who are of childbearing potential, need to use effective contraception to avoid pregnancy, and in the event of pregnancy, early pregnancy termination is recommended.⁶ While these recommendations may be medically justifiable, some patients and groups consider pregnancy termination to be morally objectionable. Thus, clinicians may be faced with a conundrum that can precipitate conflicts between patient, family, and health-care providers.^{7,8}

Recent advances in the diagnosis and medical management of patients with PAH have led to improvements in symptoms, exercise tolerance, and survival.^{9,10} However, the exclusion of pregnant patients from clinical trials has limited our understanding of the impact of these therapies on maternal-fetal well-being. Reports from single centers describing the use of PAH-specific medical therapies in pregnant patients with PAH suggest that successful outcomes are possible with careful peripartum administration of calcium channel blockers, prostacyclin analogs, and/or phosphodiesterase inhibitors.¹¹⁻¹⁶ Furthermore, a retrospective comparison of the outcomes of published cases of parturients with pulmonary hypertension managed in two eras (before [1978-1996] and after [1997-2007] the widespread commercial availability of PAH-specific therapies) reported a decline in pregnancy-associated maternal mortality in the latter era.¹⁶ These reports are encouraging; however, the failure to include patients undergoing early termination fails to fully inform the risks and benefits of therapy. Moreover, reports are likely to be subject to reporter bias, whereby poor outcomes are underreported. To better understand the impact of PAH on pregnancy outcomes in the modern era, we collected data between 1999 and 2009 from five US medical centers. Our aim was to examine maternal and fetal outcomes in pregnant patients with PAH, treated either with early surgical termination or with PAH-specific therapies, to determine the clinical outcomes associated with each of these approaches.

MATERIALS AND METHODS

We identified pregnant patients with PAH treated between January 1999 through January 2009 at LSU Health New Orleans, The University of Texas Medical Branch at Galveston, Baylor College of Medicine, The University of Texas Southwestern Medical Center, and St. Joseph's Hospital and Medical Center. Pregnant patients with PAH were identified through a review of each center's

pulmonary hypertension database and included all patients with a confirmed diagnosis of PAH who either underwent pregnancy termination or who were managed to parturition. A diagnosis of PAH was established by clinical history, physical examination, echocardiography, and right-sided heart catheterization. Right-sided heart catheterization was performed at the time of referral or within the preceding 5 years. Patients with preexisting cardiomyopathy, left ventricular ejection fraction < 40%, or mitral or aortic valve disease were excluded. Medical records were reviewed and data collected regarding demographics, gestational age at presentation, echocardiographic and hemodynamic measurements, PAH-specific therapy, manner of delivery, anesthetic agent administered, complications, and maternal-fetal outcomes. Approval to conduct this research was obtained by the respective institutional review board (IRB) at each medical center (The University of Texas Medical Branch at Galveston [IRB No. 08-115], The University of Texas Southwestern Medical Center [IRB No. STU 102010-046], Baylor College of Medicine [IRB No. 21008], LSU Health New Orleans [IRB No. 7124], St. Joseph's Hospital and Medical Center [IRB No. 11IM023]).

Continuous variables were expressed as mean $\pm$ SD or medians with ranges. Comparison of continuous parameters was performed using the Student *t* test. Dichotomous variables were analyzed using χ^2 or the Fisher exact test. A *P* value $\leq .05$ was considered significant. Data analysis was performed using Sigmaplot 3.5 (Systat Software, a subsidiary of Cranes Software International Ltd).

RESULTS

Eighteen pregnant patients with PAH were identified at the five participating centers. Patients received care from multidisciplinary teams consisting of high-risk obstetricians and nurses, anesthesiologists, neonatologists, and PAH physician specialists. Of the 18 patients, 12 elected to continue their pregnancies and six chose to undergo pregnancy termination. The mean age of the parturition and pregnancy termination groups was similar: 26.7 ± 5.6 years and 25.5 ± 6.6 years, respectively. Fifty percent of patients in the parturition group were diagnosed with PAH associated with congenital heart disease (Table 1), while the pregnancy termination group consisted of three with idiopathic PAH, two with congenital heart disease, and one with stimulant-induced PAH (Table 2). Compared with the parturition group, those in the termination group were diagnosed with PAH for a shorter period of time: 12.5 ± 10.6 years and 3.3 ± 2.5 years, respectively. Fifteen patients were diagnosed with PAH before becoming pregnant, while three patients were newly diagnosed at 25.3 ± 4.9 weeks gestation. Ten of 18 women received PAH-specific therapy prior to becoming pregnant: five in the termination group and five in the parturition group. Mean referral time for high-risk obstetric care was 16.3 ± 3.0 weeks for the parturition group and 12.7 ± 0.7 weeks for the termination group.

Six women previously diagnosed with PAH elected to undergo pregnancy termination: five were primigravida and one was multigravida. In these six patients,

Table 1—Characteristics of Parturients

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Age, y	34	35	19	30	22	32	31	21	25	24	27	20
Diagnosis	CTD	iPAH	iPAH	CTD	CHD	CHD	CHD	CHD	CHD	iPAH	CHD	iPAH
PAH, y	11	0	0	2	17	0	29	19	23	12	27	10
Therapy	ERA	...	...	P	...	...	...	...	ERA	ERA	...	CCB
WHO FC	III	III	IV	II	III	III	III	II	II	III	III	III
BP, mm Hg	150/87	91/50	107/55	111/60	107/70	130/70	92/50	100/75	106/80	110/70	120/65	105/60
RA, mm Hg	...	13	10	10	...	10	...	5	4	6	...	7
PAP, mm Hg	...	75/35	85/45	45/20	...	126/66	...	64/22	65/23	90/45	...	65/30
PCWP, mm Hg	...	15	15	11	...	15	...	6	8	8	...	6
CO, L/min	...	4	8.9	5	...	6.7	...	5.7	4.7	5.8	...	5.3

Maternal age at presentation. Diagnosis: BP = systemic BP; CCB = calcium channel blocker; CHD = congenital heart disease; CO = cardiac output; CTD = connective tissue disease; ERA = endothelin receptor antagonist; iPAH = idiopathic pulmonary arterial hypertension; P = prostaglandin analog; PAH, y = years diagnosed with pulmonary arterial hypertension; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RA = right atrial pressure; Therapy = prepartum PAH therapy; WHO FC = World Health Organization functional class.

the right ventricular systolic pressure (RVSP) estimated by echocardiography at time of referral was 90 ± 16 mm Hg. At time of referral, the World Health Organization (WHO) functional status was class I for one, class II for three, and class III for two patients (Table 2). Treatment at time of referral consisted of bosentan (Tracleer; Actelion Pharmaceuticals US, Inc), bosentan and sildenafil (Revatio; Pfizer Inc), bosentan and epoprostenol (Flolan; GlaxoSmithKline plc), or no therapy. All patients underwent dilatation and suction curettage using conscious sedation at mean gestational age of 13 ± 1.0 weeks without need for additional PAH therapy. No maternal deaths or complications were observed.

The 12 patients electing to continue with pregnancy after advice regarding the risks associated with childbirth were referred for high-risk obstetric care (Table 1). These patients consisted of eight primigravida, two secundigravida, and two multigravida. At time of referral, the WHO functional status was class II (three patients), class III (eight patients), and class IV (one patient). Their RVSP estimated by echocardiography was 82 ± 5 mm Hg. Eight of 12 patients (66%) underwent right-sided heart catheterization at time of hospital admission (mean pulmonary artery pres-

sure 49.4 ± 18.4 mm Hg and mean cardiac output 5.7 ± 1.5 L/min).

Parturients required hospitalization at 29 ± 1.4 weeks for worsening dyspnea (12 of 12), dizziness (nine of 12), chest pressure (five of 12), and/or syncope (three of 12). Endothelin receptors antagonists, previously prescribed to three patients, were discontinued early in the first trimester. Initially, nine of these patients received PAH-specific therapy that consisted of sildenafil ($n = 3$), IV prostanoid ($n = 5$), or combination therapy ($n = 1$) (Table 3). Patients initiated on prostacyclin analogs had the dose gradually increased prior to delivery and the dose was maintained during parturition and postpartum. At parturition, PAH therapy consisted of sildenafil ($n = 1$), IV prostanoid ($n = 5$), and combination therapy ($n = 3$). Three patients did not receive PAH-specific therapy at any time during pregnancy. All 12 parturients received subcutaneous anticoagulation for DVT prophylaxis and were on fluid restriction weeks before delivery. Hemodynamic monitoring with intraarterial and central venous catheters was performed during 10 deliveries, and a pulmonary artery catheter was used during a single delivery. Cesarean section was performed in 12 cases at a median of 34 weeks (range, 28-36) using epidural ($n = 8$) or general anesthesia ($n = 3$).

Maternal complications during labor consisted of hypotension in four patients (33%) requiring IV norepinephrine. One patient not receiving PAH-specific therapy died at week 29 after development of acute hypotension requiring cardiorespiratory resuscitation and emergent Cesarean section (patient 7). The median ICU length of stay for the parturition group was 2 days (range, 1-8) and the median hospital length of stay was 9 days (range, 6-28). Eleven patients (92%) were discharged alive from the hospital with a diuretic, IV prostacyclin analog ($n = 3$), bosentan ($n = 3$), sildenafil ($n = 3$), nifedipine ($n = 1$), or epoprostenol and sildenafil ($n = 1$). Antenatal parenteral

Table 2—Characteristics of Patients With Pregnancy Termination

Patient	1	2	3	4	5	6
Age, y	25	25	24	23	18	38
Diagnosis	CHD	CHD	iPAH	iPAH	iPAH	Stimulant
PAH, y	2	8	2	1	3	4
Therapy	ERA	ERA	ERA	...	ERA	ERA
	PD	PD	P			
WHO FC	III	II	II	III	II	I
RVSP, mm Hg	70	100	85	100	110	75
Termination, wk	14	14	10	14	12	12

PD = phosphodiesterase inhibitor; RVSP = right ventricular systolic pressure. See Table 1 for expansion of other abbreviations.

Table 3—Management and Outcomes of Parturients

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Initial PAH therapy	S	Epo	S, Epo	Epo	...	Epo	...	...	Tre	Epo	S	S
Start PAH therapy, wk	6	32	29	...	N	27	N	N	27	19	24	27
Dose-initial sildenafil, mg	25	...	20	...	...	...	...	...	...	...	20	20
Prostanoid, ng/kg/min	...	2	2	58	...	2	...	...	1	1	...	...
Additional PAH therapy and start time	...	...	...	...	...	...	...	...	...	...	Epo 25 wk	Epo 29 wk
Dose-labor and delivery sildenafil, mg	50	...	20	...	...	...	...	...	...	...	20	20
Prostanoid, ng/kg/min	...	10	8	58	...	14	...	...	22	6	4	4
Delivery, wk	34	36	36	32	32	28	29	34	36	32	34	36
Anesthesia	G	Epi	Epi	Epi	Epi	G	...	G	Epi	Epi	Epi	Epi
Vasopressor	...	...	...	+	...	+	+	...	+	...	...	...
Maternal outcome at hospital discharge	A	A	A	A	A	A	D	A	A	A	A	A
Discharge PAH therapy	S	Epo	S	Epo	Era	Epo	...	Era	S, Tre	Era	S	S, CCB

A = alive; D = deceased; Epi = epidural; Epo = epoprostenol; G = general; N = none, no PAH therapy; S = sildenafil; Tre = treprostinil. See Table 1 for expansion of other abbreviations.

prostacyclins were initiated for long-term treatment; however, several patients were resistant to being discharged on a continuous infusion regimen. Coincidentally, these patients were on low-dose epoprostenol infusions. Therefore, sildenafil and diuretics were continued while the prostanoid infusion was gradually reduced and the patient was closely monitored (see e-Appendix 1). Two months follow-up revealed one postpartum death 6 weeks after discharge due to bacterial sepsis (patient 6). Among the 12 deliveries, no fetal deaths occurred. The 10 male and two female infants had a median hospital stay of 11 days (range, 5-49).

DISCUSSION

In the current case series, multidisciplinary care was provided to 18 pregnant patients with PAH, six (33%) of whom underwent first trimester pregnancy termination. None of these six patients experienced maternal complications. In contrast, 12 women electing to continue their pregnancies received medical care that included daily fluid restriction, diuretics, supplemental oxygen, and prophylactic anticoagulation. Nine parturients (75%) received PAH-specific therapy several weeks prior to delivery. The parturition group mortality was 16.7%, including one hospital death in a patient not receiving PAH therapy and one postpartum death due to sepsis. Our findings suggest that early pregnancy termination is associated with a lower frequency of maternal complications and hospital mortality compared with delayed Cesarean section. Our maternal mortality was lower than previously reported for patients managed to parturition.^{3,5,16} The lower maternal mortality may be related to early diagnosis with prompt referral to an experienced center and management that involved early termination or antepartum initiation of PAH therapy.

Pregnancy is associated with physiologic changes of the maternal cardiovascular system that begin in the first trimester and continue weeks into the postpartum period.^{17,18} For example, by the third trimester, maternal cardiac output and plasma volume increase by 30% to 50% above pregestational levels.^{17,18} Notably, during vaginal delivery, Valsalva maneuvers and pain can increase heart rate and vascular resistances. Furthermore, in the hours and days after childbirth, blood volume is increased by autotransfusion of blood from the contracting uterus and shifting of peripheral edema from the extravascular compartment into the systemic vasculature. In healthy subjects, these physiologic changes are normally well tolerated, but in the presence of severe pulmonary vascular disease, hemodynamic instability may develop leading to cardiorespiratory failure or sudden death.^{19,20} Parturition and the first postpartum week have been recognized as vulnerable periods for patients with PAH.^{3,5,11,16,21} We observed one episode of sudden death in the second trimester, while three additional patients required vasopressors for hypotension during labor. Hypotension may be related to blood loss, anesthetic agents, progressive right ventricular failure, or pulmonary embolism. Management of pulmonary hypertension and right ventricular failure has been outlined as optimization of right ventricular preload and systolic function, reduction in pulmonary vascular resistance, and maintenance of aortic root pressure to allow sufficient right coronary artery filling of the right ventricle.²² Presently, there is no consensus addressing specific hemodynamic therapy in management of patients with chronic pulmonary hypertension, right ventricular failure, and hypotension. However, a recent review of animal and human data suggests that hemodynamic support in right ventricular failure and hypotension may be managed with norepinephrine and/or low-dose dobutamine (<5 µg/kg/min).²²

Recognition that pulmonary hypertension may worsen during pregnancy has led to implementation of nonpharmacologic and pharmacologic therapies. An important nonpharmacologic therapy involves limiting sodium and fluid intake.^{11,23} Limiting daily fluids to 1.5-2 L/day, restricting sodium intake, and administering diuretics in the third trimester can reduce right ventricular overdistention and avoid cardiac decompensation. As for pharmacologic therapies, prophylactic anticoagulation with heparin or low-molecular-weight heparin reduces the risk of venous thromboembolism. Early use of PAH-specific therapies such as prostacyclin analogs and phosphodiesterase-5 inhibitors has been shown to improve exercise capacity and symptoms and prevent clinical worsening in nonpregnant patients with PAH.^{24,25} A case series from England described the use of inhaled iloprost in 10 consecutive parturients with PAH.²⁶ PAH therapy was initiated at 27 weeks and delivery occurred at 34 weeks with one maternal death 4 weeks postpartum due to iloprost self-discontinuation. Thus, early institution of PAH-targeted therapies and early delivery appear to be important management strategies. In our series, nine parturients received PAH-specific therapy at a median of 29 weeks with Cesarean section performed at median of 34 weeks and no observed hospital deaths. Although there have been successful outcomes without the use of PAH therapies,¹⁶ it appears as though delayed treatment is more likely to be associated with complications.^{5,11} In our series, there was one death among three patients in the parturition group who received nonpharmacologic management but who did not receive PAH-specific therapy (patients 5, 7, 8).

The decision regarding the time and manner of delivery depend on a balance of maternal and fetal health. Due to concern that PAH may worsen as pregnancy progresses and because labor onset is unpredictable, delivery is usually timed as early as fetal maturation will permit. During labor and delivery, continuous monitoring of ECG, pulse oximetry, and intraarterial BP should be routine. While pulmonary artery catheterization may be of benefit in selected cases, there is no consensus regarding its routine use.^{16,21} In the current series, one patient was managed with a pulmonary arterial catheter while 11 were managed with intraarterial and central venous catheters. Regarding the manner of delivery, frequent use of planned Cesarean section has been described.^{16,27} While vaginal delivery is usually associated with fewer bleeding complications and infections, Cesarean section avoids prolonged labor and allows for careful preparation of anesthesia, optimization of hemodynamics, and development of contingency plans. Moreover, Cesarean section does not appear to negatively influence patient outcomes.^{16,23} Regional anesthesia is generally pre-

ferred over general anesthesia because the former has less of an effect on systemic vascular tone and cardiac function.²⁸ A higher maternal mortality has been associated with general anesthesia and improved outcomes with use of neuroaxial anesthesia.¹⁶ We noted fewer complications with neuroaxial anesthesia with avoidance of bolus administration and early epidural placement with gradual up titration of the continuous infusion.

While maternal outcomes for patients with PAH appear improved over the last several decades, the importance of preconceptual counseling and use of contraception cannot be overstated.²⁹ Counseling should include discussion about the potential teratogenic effects of endothelin receptor antagonists as well as the interaction of hormonal contraceptives and bosentan that may decrease serum contraceptive levels and make hormonal birth control less effective. Because many pregnancies are unintended or some women with PAH choose to become pregnant, it is necessary for physicians to reeducate patients about the risks and benefits associated with therapeutic abortion and continued pregnancy.³⁰ Three reports of pregnancy termination in women with PAH indicate a low risk of maternal complications.^{5,31,32} Similarly, we observed pregnancy termination to be safe and not associated with significant maternal risks. The present series provides information to clinicians about the safety of early surgical abortion and may aid to facilitate the decision-making process. Moreover, discussion of therapeutic abortion, using a shared decision model, has been proposed to establish a shared set of goals and optimize maternal medical care.³⁰

Over the past several decades, mortality associated with pregnancy and pulmonary vascular disease has declined from 30% to 56% to 17% to 33% as noted in a systematic review of 48 published cases.¹⁶ However, publication bias or failure to report poor outcomes limits the interpretation of the review. Recently, Kiely and colleagues²⁶ described their single-center experience using a similar pharmacologic and surgical approach that was associated with 11% mortality in 10 consecutive pregnancies. Similarly, we found one death (8.3%) in the antenatal period and an additional death 2 months later (16.7%) in 12 parturients. Our series is unique in that patients were managed at separate centers with each one using a different, institutional protocol. However, the five participating centers shared similar management principles that included development of a multidisciplinary team, early counseling regarding the risks of continued pregnancy, institution of fluid restriction and diuretic use along with salt avoidance, early use of PAH-specific therapies, scheduled Cesarean section, and continued postpartum treatment. The management strategy

resulted in improved patient outcomes and the experience may be generalized at other referral centers. Notably, improved patient outcomes should not be attributed to one specific intervention, such as use of a particular PAH-specific therapy, but rather related to implementation of this management strategy.

Study limitations concern the retrospective nature and relatively small number of patients reported. However, our series reported all pregnant patients with PAH, thus, recall bias or reporting bias are unlikely. Furthermore, other case series are hampered by the small number of pregnant patients with PAH^{5,11,26} while our report contains the largest series to date. Another limitation concerns our lack of control regarding PAH therapy administration. Moreover, we were unable to determine the rationale whereby physicians and patients chose to undergo termination or decided to receive or not receive PAH-specific therapy. Unfortunately, prospective, controlled clinical trials comparing various management strategies in pregnant patients with PAH are unlikely to be performed in the foreseeable future. Further clinical information may be obtained from long-term follow up of patients enrolled in multicenter registries as there is a need to further improve our understanding and treatment of these complex patients.

In summary, successful outcomes require planning and regular communication among members of a multidisciplinary team at experienced centers. In our series, early pregnancy termination was not associated with maternal complications. For patients continuing pregnancy, it is important to establish structured meetings with obstetricians, cardiac anesthesiologists, and PAH physicians to create a management strategy with contingency plans. The strategy should include aggressive antenatal fluid restriction, treatment with diuretics, prophylactic anticoagulation, and early initiation of PAH-specific therapy. Moreover, establishment of a scheduled date to prepare for a complicated delivery is important. Lastly, PAH physicians need to remain actively involved in the postpartum period including the months following hospital discharge. However, because maternal morbidity and mortality remain significant, patients should continue to receive counseling concerning contraception and avoidance of pregnancy.

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Dr Duarte: contributed to study design, data interpretation and statistical analysis of the data, drafting of the submitted manuscript, and approval of the final manuscript.

Dr Thomas: contributed to data acquisition, data interpretation, statistical analysis of the data, and approval of the final manuscript.

Dr Safdar: contributed to data acquisition, data interpretation, drafting of the submitted manuscript, and approval of the final manuscript.

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Dr deBoisblanc: contributed to data acquisition, data interpretation, drafting of the submitted manuscript, and approval of the final manuscript.

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Additional information: The e-Appendix can be found in the "Supplemental Materials" area of the online article.

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