

Severe Pulmonary Hypertension during Pregnancy

Mode of Delivery and Anesthetic Management of 15 Consecutive Cases

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Background: Available literature on pregnant women with severe pulmonary hypertension (PH) relies mainly on anecdotal case reports and two series only.

Methods: The authors reviewed the charts of all pregnant women with severe PH who were followed up at their institution during the past 10 yr, to assess the multidisciplinary treatment and outcome of these patients.

Results: Fifteen pregnancies in 14 women with severe PH were managed during this period: There were 4 cases of idiopathic pulmonary arterial hypertension (PAH), 6 cases of congenital heart disease-associated PAH, 1 case of fenfluramine-associated PAH, 1 case of mixed connective tissue-associated PAH, 1 case of human immunodeficiency virus-associated PAH, and 2 cases of chronic thromboembolic PH. PH presented during pregnancy in 3 patients. Two patients died before delivery at 12 and 23 weeks' gestation. Four patients had vaginal deliveries with regional anesthesia: One died 3 months postpartum, one worsened, and two remained stable. Four had cesarean deliveries during general anesthesia: One died 3 weeks postpartum, one worsened, and two remained stable. Five had cesarean deliveries during low-dose combined spinal-epidural anesthesia: One died 1 week postpartum, and four remained stable. There were two fetal deaths: one related to therapeutic abortion at 21 weeks' gestation and one stillbirth at 36 weeks' gestation followed by the death of the mother 1 week later.

Conclusions: Despite the most modern treatment efforts, the maternal mortality was 36%. Scheduled cesarean delivery during combined spinal-epidural anesthesia seemed to be an attractive approach, but there was no evidence of actual benefit.

Therefore, pregnancy must still be discouraged in patients with severe PH.

PULMONARY hypertension (PH) is defined by a mean pulmonary arterial pressure higher than 25 mmHg at rest, associated with a pulmonary capillary wedge pressure lower than 12 mmHg diagnosed by right heart catheterization.¹ The increased blood pressure in the pulmonary vessels ultimately leads to hypertrophy and failure of the right ventricle.² During pregnancy, physiologic cardiovascular and pulmonary changes worsen PH and right ventricular dysfunction. Additional hemodynamic changes occur with labor, especially during uterine contractions. After placental extraction, cardiac output and systemic vascular resistances increase dramatically; return to the previous state can take up to 6 months.³ Therefore, physiologic changes during pregnancy but also during delivery and the postpartum period are critical for patients with severe PH.^{3,4} Accordingly, pregnancy is considered to be contraindicated in women with PH, and an effective method of contraception is recommended in women of childbearing age.⁵

Currently, the improved medical care of patients with PH has increased their life expectancy and has resulted in more women of childbearing age considering pregnancy.² In addition, recent case reports describing good maternal and neonatal outcomes⁶⁻¹² may suggest that advances in the multidisciplinary approach have decreased the high mortality rate previously reported in two series.^{13,14} It is therefore important to provide a new series of consecutive parturients with severe PH. This should help in counseling patients with PH before they become pregnant and also give new insights into cardiopulmonary, obstetric, and anesthetic management during pregnancy, delivery, and the postpartum period.

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Materials and Methods

We reviewed the charts of all pregnant women who were followed up at our institution (tertiary referral center) from 1992 to 2002 either for a known history of PH or for PH diagnosed during their pregnancy. Institutional review board (Kremlin-Bicêtre, France) approval was obtained. Our institutional review board did not require written, informed consent because the patient treatment recorded was the one in use clinically. We collected the following information: maternal age, PH etiology,¹⁵ and treatment before pregnancy. The assess-

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Received from the Department of Anesthesiology and Intensive Care, Antoine Beclere Hospital-APHP, Clamart, France. Submitted for publication July 1, 2004. Accepted for publication February 28, 2005. Support was provided solely from institutional and/or departmental sources. Presented in part at the Annual Meeting of the European Society of Anaesthesiology, Glasgow, Scotland, June 1, 2003.

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Table 1. PH Assessment before and during Pregnancy

Case	PH Category	Before Pregnancy		During Pregnancy	
		NYHA Class	Treatment	NYHA Class	Clinical State
1	IPAH	NA	None	II	Worsening
2	IPAH	NA	None	IV	Circulatory collapse
3	IPAH	III	None	IV	Circulatory collapse and death at 12 wk
4	IPAH	I	Diltiazem	I	Stable
5	CHD-PAH	III	Oxygen and venesections	III	Cyanosis
6	CHD-PAH	I	Digoxin	I	Stable
7	CHD-PAH	I	None	I	Stable
8	CHD-PAH	II or III	Beraprost, aspirin, lisinopril	III	Hemoptysis
9	CHD-PAH	I	Digoxin	II	Hemoptysis
10	CHD-PAH	II	None	II	Stable
11	F-PAH	NA	None	IV	Circulatory collapse and death at 23 wk
12	MCTD-PAH	NA	None	IV	Worsening
13	HIV-PAH	II	None	II	Stable
14	CTEPH	I	Warfarin	II	Worsening
15	CTEPH	II or III	Warfarin	IV	Hemodynamic instability

CHD-PAH = congenital heart disease-associated pulmonary artery hypertension; CTEPH = chronic thromboembolic pulmonary hypertension; F-PAH = fenfluramine-associated pulmonary artery hypertension; HIV-PAH = human immunodeficiency virus-associated pulmonary artery hypertension; IPAH = idiopathic pulmonary artery hypertension; MCTD-PAH = mixed connective tissue disease-associated pulmonary artery hypertension; NA = not applicable (because pulmonary hypertension was revealed during pregnancy); NYHA = New York Heart Association; PH = pulmonary hypertension.

ment of PH was recorded before, during, and after pregnancy using clinical and hemodynamic criteria. Clinical evaluation was made using New York Heart Association classification, PH functional signs (dyspnea, chest pain, palpitations, syncopes, hemoptysis, cyanosis), and right heart failure signs. Hemodynamic evaluation was based whenever possible on measurement of right arterial pressures and cardiac output by right heart catheterization; echocardiographic assessment was recorded when done. Mode of delivery (vaginal or cesarean), gestational age, anesthetic management (general or regional), and intrapartum monitoring were also noted. Specific long-term treatment (prostanoids, calcium channel blockers, oral anticoagulants) was checked at each step (*i.e.*, before, during and after pregnancy), and medications given anew during delivery were recorded (transfusion, vasopressors, nitric oxide, prostanoids). We also collected information on the immediate postpartum clinical state, the hemodynamic data at the postnatal visit when available, and the final maternal outcome 1 yr after delivery. Neonatal evaluation included Apgar scores and birth weight. Neonatal mortality rate was also reported.

Individual data are provided in tables for each case. Percentages, means, or medians (with extremes in brackets) are used as indicated in the Results section.

Results

Fifteen consecutive cases of pregnancies in 14 patients with severe PH were managed. One patient had two pregnancies 6 yr apart. The mean age was 32 (22–41) yr. The median parity was 0 (0–3). There were 4 cases of idiopathic pulmonary arterial hypertension (IPAH), 6

cases of congenital heart disease-associated pulmonary arterial hypertension (PAH; formerly Eisenmenger syndrome), 1 case of fenfluramine-associated PAH, 1 case of mixed connective tissue-associated PAH, 1 case of human immunodeficiency virus-associated PAH, and 2 cases of chronic thromboembolic PH (table 1).

Two patients were hospitalized early, at 12 and 23 weeks' gestation, because of acute hemodynamic instability. Both deteriorated quickly in the intensive care unit and died before a therapeutic abortion could be performed. Five women only remained stable throughout pregnancy (table 1). One patient had a therapeutic abortion at 21 weeks' gestation and improved subsequently (table 2).

There were four vaginal deliveries, all performed during regional analgesia. Four cesarean deliveries were performed during general anesthesia. Five cesarean deliveries were performed during low-dose combined spinal-epidural anesthesia. During delivery, nitric oxide or vasopressor support or both were given in 5 of the 13 cases (table 2).

Maternal outcome after delivery is given in table 2. Intravenous epoprostenol treatment was introduced in two cases in the initial postpartum period. There were three additional deaths at 1 week, 3 weeks, and 3 months postpartum (table 2).

Two fetal deaths occurred along with the maternal deaths before delivery; the two others were related to therapeutic abortion and stillbirth. The mean gestational age of the 11 live neonates was 35 (32–40) weeks, and the mean birth weight was 2,360 (1,140–3,500) g. The median Apgar scores were 10 (9–10) at 1 min and 10 (10–10) at 5 min.

Table 2. Delivery Management and Maternal Outcome

Case	GA, wk	Delivery Management			Outcome	
		Obstetric	Anesthetic	New Medications	Immediate Postpartum	1 yr Later
1	37	CD	GA		Stable	Improvement
2	33	Induced labor and VD	EA	Furosemide, epoprostenol, dobutamine	Worsening	Death 3 months postpartum
4	37	CD	GA		Stable	Stable
5	32	CD	CSE	NO and PEs	Stable	Stable
6	40	VD	CSA		Stable	Stable
7	36	Breech VD	EA		Worsening	Stable
8	34	CD	CSE	NO	Stable	Stable
9	38	CD	CSE		Stable	Stable
10	36	CD after stillbirth	CSE	PEs and platelets	Worsening	Death 1 week postpartum
12	21	Induced labor and vaginal TA	EA	NO Dobutamine	Improvement	Stable
13	34	CD	CSE	AZT, HEA,* norepinephrine	Stable	Stable
14	33	Placenta previa and CD	GA	PEs	Worsening	Thromboendarterectomy,* PAP normalization
15	33	CD	GA		Worsening	Death 3 weeks postpartum

* See details in Web Enhancement.

AZT = zidovudine; CD = cesarean delivery; CSA = continuous spinal analgesia; CSE = combined spinal-epidural anesthesia; EA = epidural analgesia/anesthesia; GA = general anesthesia; GA = gestational age; HEA = hydroxyethyl starch; immediate postpartum = first days in intensive care unit; NO = nitric oxide; PAP = pulmonary arterial pressure; PEs = packed erythrocytes; TA = therapeutic abortion; VD = vaginal delivery.

Additional information regarding the results is available on the ANESTHESIOLOGY Web site at <http://www.anesthesiology.org>.*

Discussion

We found a 36% overall maternal mortality rate (5 of 14 patients), which is in accordance with the 30–50% mortality rate reported previously.^{13,14,16} Because we assessed a series of consecutive cases, a selection bias is less likely to have occurred than in gathered case reports or series obtained from postal questionnaires. From this study and the previous literature, it remains unclear whether pregnancy and delivery are actually better tolerated in congenital heart disease-associated PAH than in IPAH.^{13,14,16}

Currently, vasodilators and antiproliferative prostanoids are the main treatment of the disease.² Nitric oxide is mainly used to assess pulmonary vasoreactivity.¹⁷ High-dose calcium channel blockers may produce improvement and sometimes normalization of pulmonary arterial pressure after long-term therapy, but in only 5–10% of IPAH patients¹⁷; a 1-yr successful therapy and a return to near-normal right ventricular function has been recommended before considering pregnancy.⁶ One woman (patient 4) was in such a situation, and she remained stable throughout pregnancy and the peripartum period. Continuous intravenous infusion of prostacyclin (epoprostenol) has demonstrated an improve-

ment of survival and quality of life in IPAH patients with functional classes III and IV.^{18,19} No recommendations are yet available during pregnancy, but there are several case reports using epoprostenol with good outcomes.^{8,11} In our series, the single patient (patient 8) receiving an oral prostacyclin analog worsened during pregnancy but then remained stable postpartum and at the 1-yr follow-up.

Deterioration of PH during pregnancy has been reported to occur between the 20th and 24th weeks of gestation, when most pregnancy-induced hemodynamic changes have occurred.^{3,4} In our series, there were three cases of early deterioration at 12, 20, and 23 weeks' gestation, which is somewhat earlier than classically mentioned above; only one patient survived, after therapeutic abortion. This confirms that early PH deterioration during pregnancy should lead to prompt therapeutic abortion.¹³ In five of the seven other cases, deterioration occurred at the beginning of the third trimester (27–33 weeks' gestation).

Mode of delivery and anesthetic management remain debated. In our series, four women had vaginal deliveries during regional analgesia: Two of them had induced labor (with a prostaglandin E and oxytocin) because they worsened and needed termination of pregnancy. It is noteworthy that prostaglandins E usually produce pulmonary vasodilatation, whereas prostaglandins F₂ α induce pulmonary vasoconstriction²⁰; very low oxytocin rates used when labor is induced seem to have no significant hemodynamic effect.²¹ If vaginal delivery is chosen, low-dose epidural analgesia is considered of paramount importance.^{6,13} It has no significant deleterious

* The Web Enhancement contains the 15 individual mini-case reports plus two tables detailing individual hemodynamic measurements and individual neonatal data.

hemodynamic effect by itself, and it considerably decreases the adverse hemodynamic consequences of labor.²¹

Nonetheless, scheduled cesarean delivery is often used.^{8,9,12,22-25} It has the advantage of taking place during the day and avoiding the risk of an urgent cesarean delivery during labor with the hemodynamic instability that could occur under such conditions. Some authors have described the use of general anesthesia with good maternal outcome.^{22,23} However, others have reported increased pulmonary arterial pressure during laryngoscopy and tracheal intubation; moreover, adverse effects of positive-pressure ventilation on venous return may ultimately lead to cardiac failure.^{26,27} There is now an increasing number of case reports highlighting the use of regional anesthesia with good outcome.^{8,9,12,24,25} Nonetheless, the dense and extended block needed to prevent pain during cesarean delivery may have significant hemodynamic consequences. Specifically, single-shot spinal anesthesia is considered contraindicated in these patients.^{26,27} Therefore, epidural anesthesia with incremental doses is most often advocated as the best regional technique.^{12,24,25} In our series, however, when we chose regional anesthesia for scheduled cesarean delivery, we preferred using combined spinal-epidural anesthesia because it provides a better sensory block than epidural anesthesia alone and no additional risk of hypotension when only a very low dose is used spinally.^{28,29}

Monitoring at delivery with electrocardiography, pulse oximetry, and invasive arterial blood pressure monitoring is always advocated.^{6,12,23-25,27} By contrast, the use of a pulmonary artery catheter is more debated because of the increased risk of pulmonary artery rupture and thrombosis in PH.^{26,30} In our series, standard vascular access included a radial artery catheter, a central venous line, and a large venous catheter for rapid fluid infusion. A pulmonary artery catheter was used in three cases (all without intracardiac shunt) along with dobutamine or norepinephrine administration. We paid more attention to the relative variations of the hemodynamic measurements than to the initial values themselves. Nitric oxide was administered only in case of acute PH exacerbation.

The postpartum period is the most critical period for acute PH decompensations.^{13,23} After placental extraction, oxytocin must be infused slowly because direct intravenous boluses of large doses can be fatal in patients with unstable hemodynamic status.³¹ Later, cardiac output and systemic vascular resistances increase dramatically. Return to the previous state takes up to 6 months, but the main changes occur during the first 2 weeks.⁴ Consequently, all of our patients received intensive care for at least several days postpartum.³² Symptomatic therapy during the postpartum period includes inhaled nitric oxide and epoprostenol infusion or inhaled iloprost.^{7,11,23} In our series, nitric oxide was not used prophylactically to avoid the problem of weaning. One

woman was already receiving chronic oral therapy with beraprost sodium, and long-term intravenous epoprostenol was introduced postpartum in three women. One of the women died 3 months postpartum, whereas the three others were found to have a stable PH 1 yr after delivery. These findings support the idea that prostanoids should be considered early during pregnancy in women with PH.^{8,11}

Anticoagulation is recommended in IPAH and chronic thromboembolic PH, but it is debated in PH of other etiologies.^{1,33} In the postpartum period, anticoagulation is widely indicated.³⁴ We aimed to achieve an activated partial thromboplastin time ratio between 1.5 and 2 within 12–24 h after delivery. If there was a thromboembolic history or a thrombophilia, the final target was set higher (2–3.5).¹

The neonatal survival rate is reported to be around 87–89% in congenital heart disease-associated PAH, IPAH, or associated forms of PAH.^{14,16} The main fetal risk is linked to maternal hypoxemia, which results in growth restriction, preterm delivery, and stillbirth.^{7,32} In our series, the neonatal survival rate was 85% (11 of 13). Four neonates were under the 10th percentile. All children had normal development during the first year of follow-up. The relatively good prognosis of the neonate contrasts with the high maternal mortality rate.⁷

In conclusion, despite the most modern treatment efforts, the overall mortality rate of pregnant women with severe PH was still 36% in this series. Cesarean delivery during regional anesthesia with invasive monitoring seemed to be an attractive approach, but there was no evidence of actual benefit. Therefore, we think that pregnancy should be still discouraged in these patients and therapeutic abortion should be offered, particularly when early deterioration occurs. If this option is not accepted, introduction of prostanoids should be considered rapidly, especially in IPAH.

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