JACC Vol. 31, No. 7
June 1998:1650–7

Outcome of Pulmonary Vascular Disease in Pregnancy: A Systematic Overview From 1978 Through 1996

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Objectives. **Published reports were reviewed to evaluate the characteristics of peripartal management and the late pregnancy outcome in women with pulmonary vascular disease (PVD).**

Background. **Pulmonary hypertension poses one of the highest risks for maternal mortality, but actual data on the maternal and neonatal prognosis in this group are lacking.**

Methods. **Reports published from 1978 through 1996 of Eisenmenger's syndrome (n = 73), primary pulmonary hypertension (PPH) (n = 27) and secondary vascular pulmonary hypertension (SVPH) (n = 25) complicating late pregnancy were included and analyzed using logistic regression analysis.**

Results. **Maternal mortality was 36% in Eisenmenger's syndrome, 30% in PPH and 56% ($p < 0.08$ vs. other two groups) in SVPH. Except for three prepartal deaths due to Eisenmenger's syndrome, all fatalities occurred within 35 days after delivery. Neonatal survival ranging from 87% to 89% was similar in the three groups. Previous pregnancies, timing of the diagnosis and hospital admission, operative delivery and diastolic pulmonary artery pressure were significant univariate ($p < 0.05$) maternal risk factors. Late diagnosis ($p = 0.002$, odds ratio 5.4) and late hospital admission ($p = 0.01$, odds ratio 1.1 per week of pregnancy) were independent predictive risk factors of maternal mortality.**

Conclusions. **In the last two decades maternal mortality was comparable in patients with Eisenmenger's syndrome and PPH; however, it was relevantly higher in SVPH. Maternal prognosis depends on the early diagnosis of PVD, early hospital admission, individually tailored treatment during pregnancy and medical therapy and care focused on the postpartal period.**

(J Am Coll Cardiol 1998;31:1650–7)

Preexistence or gestational occurrence of pulmonary vascular disease (PVD) is one of the rare conditions unequivocally considered to pose an extreme risk of maternal death. The poor tolerance during pregnancy seems to result from a low, pregnancy-independent exercise capacity superimposed on the gestational cardiovascular demands, insufficient adaptation of the right heart and poorly compliant pulmonary vasculature (1–5). Pregnancy prevention and early interruption became and still are the relevant measures for improving long-term survival in women of childbearing age with PVD (6). The last large-scale review of outcome in pregnant women with Eisenmenger's syndrome was published in 1979 (7); however, actual data on the outcome of late pregnancy in women with other types of PVD are lacking. Published reports from the two decades were reviewed to evaluate the influence of peripartal management and outcome of late pregnancy in women with PVD.

Methods

Material selection. The data base of the National Library of Medicine (MEDLINE) was used to identify the cases, published in any language from January 1978 to December 1996, of PVD complicating late pregnancy. The key words *pregnancy, pulmonary hypertension, primary pulmonary hypertension* (PPH), *pulmonary vasculitis, pulmonary vascular disease, congenital heart disease, Eisenmenger's complex* and *Eisenmenger's syndrome* were used. The reference list of all journal articles and recent book chapters was reviewed. The cases of late pregnancy (beyond 22 weeks and described with the intention to continue the pregnancy) were separated from reports of spontaneous abortion or pregnancy interruption. Only the last reported pregnancy was included in the analysis. Other types of secondary PVD (e.g., acquired heart, chronic lung or chest wall diseases) were rejected on an a priori basis. Eisenmenger's syndrome was considered if congenital heart disease, a shunt at any level and pulmonary hypertension (irrespective of the numerical values) were present. From one monocentric study (8), only patients with an established diagnosis were included; other cases, reported years before the definitive diagnosis was made, were excluded (8). PPH was considered if none of the concomitant causes, diseases or assumed triggers of pulmonary hypertension (9) was mentioned. Secondary vascular pulmonary hypertension (SVPH) comprised a heterogeneous group of patients with the history

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Manuscript received September 17, 1997; revised manuscript received February 23, 1998, accepted March 4, 1998.

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Published by Elsevier Science Inc.

0735-1097/98/$19.00
PII S0735-1097(98)00162-4

Abbreviations and Acronyms

CI = confidence interval
OR = odds ratio
PAP = pulmonary artery pressure
PPH = primary pulmonary hypertension
PVD = pulmonary vascular disease
Sa_{O_2} = arterial oxygen saturation of hemoglobin
SVPH = secondary vascular pulmonary hypertension

or presence of various concomitant diseases, assumed or recognized triggers and/or autopsy findings of PVD. In some, pulmonary hypertension was connected with the use of incriminated drugs, in others it was of congenital origin (peripheral pulmonary artery stenoses) or resulted from thromboembolism, hepatitis, systemic connective tissue or vascular inflammatory disease. These cases were grouped together independent of etiopathogenesis of PVD and labeled SVPH.

Data analysis. Patient characteristics were presented for each group, and the details of peripartal management were separated by maternal outcome. Data were presented as the number (%) per group, mean value ± SD and range or, when appropriate, as median and range. Maternal and fetal/neonatal mortality or survival were presented as the number (%) of deaths and exact 95% confidence intervals (CI) for each PVD group. Logistic regression analysis (SPSS for Windows, Release 6.0.1., SPSS Inc.), with maternal outcome as the dependent variable, was used univariately for each group and for all cases. Independent covariates included age, gravida, para, timing of the diagnosis (before pregnancy vs. late diagnosis, if PVD was found during pregnancy or after delivery), week of pregnancy at hospital admission, pulmonary artery pressure (PAP), hemoglobin and arterial oxygen saturation of hemoglobin (Sa_{O_2}) values during pregnancy, timing of delivery, mode of delivery (vaginal vs. operative), type of monitoring (invasive vs. noninvasive), type of anesthesia (general vs. regional) and use or nonuse of a pulmonary artery catheter, oxytocic drugs and antithrombotic drugs. When neonatal outcome was analyzed as the dependent variable, maternal outcome was included in the independent covariates. A p value <0.1 indicated a trend or potential risk factor. A p value <0.05 was considered statistically significant, and the odds ratio (OR) with 95% CI was calculated to express the predictive relative risk. For continuous and counting data, risk was expressed per unit of measurement. Multivariate (stepwise forward) logistic regression analysis was used to identify the independent risk factors of maternal mortality. The limit to enter an item into the multivariate analysis was $p < 0.05$ in the univariate analysis.

Results

Eisenmenger's syndrome. The patient characteristics (8,10–60) are summarized in Table 1, and the anatomic defects are presented in Table 2. Worsening of dyspnea and cyanosis and, occasionally, hemoptysis, cerebrovascular attack, syncope, chest pain, atrial fibrillation or premature uterine contractions were indications for hospital admission during pregnancy. Treatment consisted of bed rest and oxygen supplementation, digoxin (rarely), calcium antagonists and, to suppress premature uterine contractions or preeclampsia, magnesium. Three patients died during pregnancy (23,41). Of 70 remaining patients, 33 (47%) delivered at term (≥37 weeks), 23 (33%) delivered between weeks 32 and 36 and 14 (20%) delivered ≤31 weeks. Peripartal management is presented in Table 3. Hypoxemia, pulmonary hypertensive crisis and systemic hypotension (in two cases due to oxytocic drugs), bradycardia, pulmonary thromboembolism, cerebrovascular attack, convulsions, bleeding with or without anticoagulant therapy, peripheral vein thrombosis and concomitant peripartal cardiomyopathy influenced postpartal recovery. Vasoactive

Table 1. Characteristics of Parturients With Pulmonary Vascular Disease

	Eisenmenger's Syndrome (n = 73)	Primary Pulmonary Hypertension (n = 27)	Secondary Vascular Pulmonary Hypertension (n = 25)
Gravida*	1 (1–4)	2 (1–3)	2 (1–7)
Para ≥1*	1 (1–3)	2 (1–3)	3 (1–5)
n (%)	17 (23%)	14 (52%)	13 (52%)
Diagnosis made†			
Before pregnancy	59 (81%)	7 (26%)	6 (24%)
During pregnancy	11 (15%)	14 (52%)	12 (48%)
Postpartum	3 (4%)	6 (22%)	7 (28%)
Hospital admission (weeks of pregnancy)‡	28.3 ± 6.7 (10–40)	27.6 ± 5.6 (15–36)	32.4 ± 5.1 (21–39)
At term before delivery†	9 (13%)§	0	6 (24%)
Sa_{O_2} (%)‡	84.8 ± 6.6 (67–98)	91.1 ± 7.0 (70–98)	91.4 ± 4.5 (82–96)
Hgb (g/dl)‡	15.7 ± 2.5 (10.2–20.4)	Not reported	11.5 ± 2.2 (8.9–15.9)
PAP, systolic (mm Hg)‡	108.0 ± 25.5 (55–160)	85.3 ± 20.4 (50–135)	82.9 ± 27.9 (30–135)
PAP, diastolic (mm Hg)‡	55.2 ± 19.7 (12–100)	44.4 ± 13.2 (25–70)	37.4 ± 17.9 (5–70)

Data presented are *median value (range); †number (%) of patients; or ‡mean value ± SD (range). §n = 70. Hgb = hemoglobin concentration during pregnancy (n = 49); PAP = pulmonary artery pressure during pregnancy (systolic value, n = 81; diastolic value, n = 70); SaO_2 = arterial oxygen saturation of hemoglobin during pregnancy (n = 73).

Table 2. Anatomic Defects of Eisenmenger's Syndrome (n = 73)

Isolated ventricular septal defect*†	35 (48%)
Isolated atrial septal defect*	13 (18%)
Isolated patent ductus arteriosus	7 (9%)
Atrial and ventricular septal defect, atrioventricular canal*	5 (7%)
Truncus arteriosus, aortopulmonary window*	3 (4%)
Patent ductus arteriosus with atrial or ventricular septal defect	2 (3%)
Transposition of the great arteries with single ventricle or atrial and ventricular septal defect*	2 (3%)
Pulmonary atresia with ventricular septal defect and aortopulmonary collateral channels	2 (3%)
Tetralogy of Fallot, Pott's anastomosis*	1 (1%)
Not defined	3 (4%)

*In nine patients a cardiac surgical procedure was performed at various intervals before pregnancy. †In four patients an isolated ventricular septal defect was surgically closed in childhood. Data presented are number (%) of patients.

drugs, oxygen supplementation, blood transfusion, cessation or start of anticoagulant therapy, reoperation and hysterectomy or repair of an atrial septal defect were required postpartum. Of 26 fatalities (36%) (Fig. 1), 23 women died within 30 days after delivery (12,13,15,21,22,24,25,27,32–35,37–41,47,51,54). The cause of death was described as pulmonary hypertensive crisis with therapy-resistant heart failure (n = 13), unspecific "sudden" death (n = 7), autopsy-confirmed pulmonary thromboembolism (n = 3), cerebral thromboembolism (n = 1) and rupture and dissection of the pulmonary artery (n = 1). Late maternal death (months postpartum) was reported in two cases. Live-born neonates (n = 66, 90%) weighed 2,112 ± 876 g. Fetal or early neonatal death due to maternal death or decompensation, intrauterine growth retardation and/or premature delivery was reported in six patients (23,26,35,41, 53,56), late neonatal death due to congenital heart disease was reported in three patients (13,28,32) and neonatal outcome of two pregnancies was not reported (22,45). The fetal/neonatal mortality rate in this group was 13% (95% CI 6 to 23).

Table 3. Management and Outcome of Pregnant Women With Eisenmenger's Syndrome (n = 73)

	Maternal Survival	Maternal Mortality
No. (%)	47 (64%)	26 (36%)‖
95% CI	52–75	25–48
Age (years)*	26.4 ± 4.8 (18–37)	24.9 ± 4.5 (18–33)
Hospital admission (weeks of pregnancy)*	26.7 ± 6.5 (10–39)	31.4 ± 5.9 (21–40)
Toxemia of pregnancy†	2 (4%)	3 (12%)
Delivery (weeks of pregnancy)*	35.1 ± 3.5 (26–40)	34.4 ± 4.4 (26–40)
Vaginal delivery†	27 (57%)	11 (48%)
Operative delivery†	20 (43%)	12 (52%)‖
Monitoring		
Noninvasive, not reported†	24 (51%)	15 (63%)
Invasive SAP and/or CVP†	23 (49%)	9 (37%)
Invasive PAP†	8 (17%)	6 (25%)
Anesthesia/analgesia		
Not reported†	13 (28%)	5 (22%)
Regional techniques†	22 (47%)	8 (35%)
General anesthesia†	12 (25%)	7 (30%)
Local anesthesia/analgesia†	0	3 (13%)
Oxytocic drugs†	14 (30%)	4 (17%)
Antithrombotic therapy†	28 (60%)	12 (46%)
Neonatal survival†	43 (96%)§	20 (77%)
95% CI	85–99	56–91
Maternal death, days postpartum (n = 23)‖	—	5 (0–30)‡

Data presented are *mean value ± SD (range); †number (%) of patients; or ‡median value (range). §In two cases neonatal outcome was not reported. ‖Three patients died before delivery and 23 died after delivery. CI = confidence interval; CVP = central venous pressure; PAP = pulmonary artery pressure; SAP = systemic arterial pressure.

Table 4. Management and Outcome of Pregnant Women With Primary Pulmonary Hypertension (n = 27)

	Maternal Survival	Maternal Mortality
No. (%)	19 (70%)	8 (30%)§
95% CI	50–86	14–50
Age (years)*	25.7 ± 5.3 (14–36)	23.3 ± 4.4 (18–31)
Hospital admission (weeks of pregnancy)*	26.9 ± 5.5 (15–36)	28.7 ± 5.9 (18–36)
Toxemia of pregnancy†	1 (5%)	0
Delivery (weeks of pregnancy)*	35.2 ± 3.9 (29–39)	33.3 ± 5.4 (26–40)
Vaginal delivery†	12 (63%)	3 (37%)
Operative delivery†	7 (37%)	5 (63%)
Monitoring		
Not reported†	8 (42%)	4 (50%)
Invasive SAP and/or CVP†	11 (58%)	4 (50%)
Invasive PAP†	9 (47%)	5 (63%)
Anesthesia/analgesia		
Not reported†	8 (42%)	2 (25%)
Regional techniques†	9 (47%)	5 (63%)
General anesthesia†	2 (11%)	1 (13%)
Oxytocic drugs†	7 (37%)	3 (37%)
Antithrombotic therapy†	6 (32%)	3 (37%)
Neonatal survival†	18 (95%)	6 (75%)
95% CI	74–100	35–97
Maternal death, days postpartum§	—	6 (2–35)‡

Data presented are *mean value ± SD (range); †number (%) of patients; or ‡median value (range). §All maternal deaths occurred postpartum. Abbreviations as in Table 3.

Primary pulmonary hypertension. The characteristics of 27 parturients (42,61–79) are summarized in Table 1. Dyspnea at rest and, less frequently, a hoarse voice, hemoptysis, syncope, cyanosis or toxemia of pregnancy indicated hospital admission during pregnancy. Treatment consisted of bed rest and oxygen supplementation, digoxin (occasionally), diuretic agents and vasodilators. Peripartal management is presented in Table 4. Eleven parturients (41%) delivered at term, 10 (37%) between 32 and 36 weeks and 6 (22%) ≤31 weeks. Two survivors delivered during hyperbaric oxygenation (76). Major postpartal complications were worsening of dyspnea, cyanosis, hemoptysis, pulmonary hypertensive crisis (in one patient after use of oxytocin) and systemic hypotension. Eight patients (30%) died (61,63,64,66,68,70,72,74), all after delivery (Fig. 1), of therapy-resistant heart failure; only in the case of venoocclusive disease were venous thrombi found at autopsy (68).

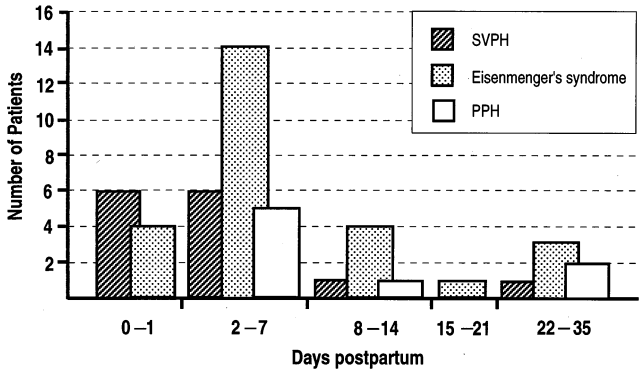

Figure 1. Time of maternal death in parturients with Eisenmenger's syndrome (n = 26), PPH (n = 8) and SVPH (n = 14). The 0–1 day postpartal period includes three patients with Eisenmenger's syndrome who died during pregnancy.

Two late deaths and two heart–lung transplantations were reported months to years after pregnancy. All neonates (weight 1,978 ± 758 g) were live-born, but three infants (11% [95% CI 2 to 29]) who were delivered prematurely (66,68,76) subsequently died.

Secondary vascular pulmonary hypertension. The characteristics of 25 parturients (42,72,80–101) are summarized in Table 1. The causes, concomitant findings or assumed triggers of SVPH were Takayasu's arteritis, pulmonary vasculitis of connective tissue (lupus erythematosus, scleroderma), sickle cell disease, illicit and appetite suppressant drugs, chronic pulmonary thromboembolism, hepatitis, dwarfism with congenital hypothyroidism and peripheral pulmonary artery stenoses. Dyspnea, syncope (rarely), chest pain, hemoptysis, systemic hypotension, toxemia of pregnancy or intrauterine growth retardation led to hospital admission during pregnancy. Bed rest and oxygen supplementation and, in a few cases, digoxin, diuretic agents, steroid therapy and nifedipine were used prepartum. All patients, except for one, delivered at ≥32 weeks (Table 5). Pulmonary hypertensive crisis after oxytocin use occurred in one patient. One parturient was treated with heparin and urokinase; operative delivery was assisted by extracorporeal circulation; and postpartal treatment with coumarin, nifedipine, prostaglandins and diuretic agents led to the patient's survival (97). All fatalities (Fig. 1) occurred after delivery (42,72,81,83,85,86,89,91–96) and were described as sudden (n = 7) or progressive (n = 7) heart failure; no evidence of new pulmonary thromboembolism was found at autopsy. Late maternal death, several months postpartum, was reported in three patients. Twenty-two neonates (weight 2,372 ± 640 g) survived. One stillbirth (81) and two neonatal deaths due to congenital anomalies (88,89) resulted in a fetal/neonatal mortality rate of 12% (95% CI 3 to 31).

Logistic regression analysis (Table 6). This analysis revealed several risk factors in the Eisenmenger's syndrome and SVPH groups and none in the PPH group. Late diagnosis of PVD and timing of hospital admission (risk increasing by 9% with each week of pregnancy) were independent risk factors of maternal mortality for all patients. Operative delivery, severity of pulmonary hypertension (diastolic rather than systolic PAP) and number of previous pregnancies and deliveries were contributing factors. Analysis of maternal mortality showed a trend toward a significant difference between the PPH and SVPH groups ($p = 0.06$) and between the Eisenmenger's syndrome and SVPH groups ($p = 0.08$). Neonatal outcome was significantly influenced by maternal outcome in patients with Eisenmenger's syndrome ($p < 0.046$, OR 4.5) and cumulatively in all patients ($p < 0.02$, OR 3.8).

Discussion

Eisenmenger's syndrome. In a review of the cases from the late 1940s to 1978, Gleicher et al. (7) found that 30% of all pregnancies in patients with Eisenmenger's syndrome resulted in maternal death. More recently, an 11% mortality rate in a London-Torino bicentric study (102); one maternal death among 26 patients in Trivandrum, India (103); and survival of all five patients in Hamilton, Ontario, Canada (42) implicate that the outcome of pregnancy in patients with Eisenmenger's syndrome generally improved. However, two maternal deaths, one abortion and one successful delivery after surgical correction of congenital heart disease were documented in four women in Memphis, Tennessee (104). Three of 10 patients with Eisenmenger's syndrome died in São Paulo, Brasil (41). The mortality rate of 36% (or 33% if six previous pregnancies

Table 5. Management and Outcome of Pregnant Women With Secondary Vascular Pulmonary Hypertension (n = 25)

	Maternal Survival	Maternal Mortality
n (%)	11 (44%)	14 (56%)§
95% CI	24–65	35–76
Age (years)*	26.1 ± 3.5 (17–30)	29.4 ± 3.9 (23–34)
Hospital admission (weeks of pregnancy)*	32.2 ± 6.3 (21–39)	32.6 ± 4.5 (24–38)
Toxemia of pregnancy†	1 (9%)	3 (21%)
Delivery (weeks of pregnancy)*	36.3 ± 2.8 (32–40)	35.9 ± 4.5 (29–39)
Vaginal delivery†	8 (73%)	4 (29%)
Operative delivery†	3 (27%)	10 (71%)
Monitoring		
Not reported†	5 (45%)	2 (14%)
Invasive SAP and/or CVP†	6 (55%)	12 (86%)
Invasive PAP†	6 (55%)	10 (71%)
Anesthesia/analgesia		
Not reported†	5 (46%)	4 (28%)
Regional techniques†	3 (27%)	5 (36%)
General anesthesia†	2 (18%)	5 (36%)
Oxytocic drugs†	4 (36%)	2 (14%)
Antithrombotic therapy†	3 (27%)	10 (71%)
Neonatal survival†	10 (91%)	12 (86%)
95% CI	59–100	57–98
Maternal death, days postpartum§	—	1 (0–30)‡

Data presented are *mean value ± SD (range); †number (%) of patients; or ‡median value (range). §All maternal deaths occurred postpartum. Abbreviations as in Table 3.

Table 6. Logistic Regression Analysis: p Value and Odds Ratio (95% confidence interval)* for Maternal Outcome as Dependent Variable

	Univariate Analysis				
Independent Covariable	Eisenmenger's Syndrome	Primary Pulmonary Hypertension	Secondary Vascular Pulmonary Hypertension	All Patients	Multivariate Analysis (all patients)
Age (year)	>0.1	>0.1	0.06	>0.1	—
Gravida (n)†	>0.1	>0.1	0.052	0.02 1.52 (1.06–2.17)	0.09
Para (n)	>0.1	>0.1	>0.1	0.06	—
Late diagnosis†	0.003 6.7 (1.8–24.5)	>0.1	>0.1	0.001 3.5 (1.6–7.5)	0.002 5.4 (2.2–13.4)
Hospital admission† (week)	0.009 1.13 (1.03–1.25)	>0.1	>0.1	0.003 1.11 (1.04–1.19)	0.01 1.09 (1.02–1.19)
PAP, systolic (mm Hg)	0.06	>0.1	>0.1	>0.1	—
PAP, diastolic (mm Hg)	0.01 1.08 (1.02–1.16)	>0.1	>0.1	0.03 1.03 (1.00–1.06)	—‡
Operative delivery†	>0.1	>0.1	0.03 6.6 (1.1–38.8)	0.02 2.4 (1.1–5.2)	0.07
Anticoagulant drug	>0.1	>0.1	0.03 6.6 (1.1–38.8)	>0.1	—

*Odds ratio and 95% confidence interval were calculated at $p < 0.05$. For continuous and counting data, the odds ratios are expressed per unit of measurement. †Gravida, late diagnosis, hospital admission and operative delivery were included in the multivariate analysis. ‡Diastolic value was excluded from the multivariate analysis owing to a high number of missing values. PAP = pulmonary artery pressure.

are included) indicates that the risks remained rather unchanged over the past two decades of experience with Eisenmenger's syndrome.

Primary versus secondary vascular pulmonary hypertension. The classification of PVD syndrome is controversial (4–6,9,67,105), and PPH is acknowledged to be a pleomorphic disease whose etiology is unclear (106). Hopkins et al. (6) recently found that a more favorable hemodynamic profile and a higher 3-year survival rate are characteristic of patients with Eisenmenger's syndrome as compared with patients with PPH. It was expected that the outcome of late pregnancy between these groups would similarly differ. However, maternal survival was comparable in patients with Eisenmenger's syndrome and the "pure form" of PPH, in contrast to the mortality rate of >50% in patients with SVPH. In addition, the outcome differences were obvious within the heterogeneous group of patients with SVPH. Pulmonary vasculitis due to systemic diseases and illicit drug abuse resulted in maternal death in almost all patients, representing the most malignant form of PVD, with poor tolerance during pregnancy and postpartal changes. On the other extreme, in Takayasu's arteritis and peripheral pulmonary artery stenoses (right ventricular and central pulmonary hypertension with protected pulmonary microcirculation), the pregnancy, delivery and postpartal period were experienced without difficulties.

General risk factors and cofactors. Patient age and history of pregnancy (Table 6) were found to represent potential risk cofactors of maternal death. Although incompletely reported and not measured at identical periods during gestation, available Sa_{O_2} and hemoglobin data failed to show any relation to the outcome in Eisenmenger's syndrome. PAP values were incompletely reported as well, and were not measured using identical methods or at the identical period of pregnancy. Possibly owing to the missing values, diastolic PAP was a stronger risk cofactor than systolic PAP in the patients with Eisenmenger's syndrome and cumulatively for all patients.

The late diagnosis of PVD and late hospital admission were the independent risk factors of mortality for patients with Eisenmenger's syndrome and cumulatively for all patients. On average, patients with Eisenmenger's syndrome and those with PPH were admitted to the hospital at the beginning of the third trimester (Tables 1, 3 and 4). The average difference in the timing of hospital admission was 5 and 2 weeks between survivors and nonsurvivors in the Eisenmenger and PPH groups, respectively. Patients with SVPH were admitted 5 weeks later, and no difference was found between survivors and nonsurvivors (Tables 1 and 5). Thus, earlier diagnosis and hospital admission and timely preparation of the medical team have favorably influenced the maternal outcome. Although the benefits of nitric oxide and prostacyclin therapy (105,106) in pregnant women with PVD remain to be confirmed, current therapeutic options look more promising than those available in the 1978–1996 period.

Management of late pregnancy and delivery. Duration of pregnancy, timing and mode of delivery, type of anesthesia or analgesia (with a preference for epidural technique) and type of maternal monitoring were similarly distributed between survivors and nonsurvivors. A pulmonary artery catheter was rarely used in patients with Eisenmenger's syndrome and more frequently in those with PPH and SVPH. The peripartal use of a pulmonary artery catheter in PVD must be questioned owing to its limited value of providing monitoring information, its higher potential for complications and its lack of influence on maternal outcome.

Operative delivery was an independent risk factor of maternal mortality in patients with SVPH and a potential risk factor for all patients (Table 6). In many patients sudden death was reported days after delivery, not as a direct consequence of the operation. Although frequently unavoidable, cesarean section should be considered a risk (co)factor as it is not the safest route for delivery (107) in parturients with PVD. The use of antithombotic drugs remains controversial. These drugs have caused bleeding, cardiovascular instability and ultimately maternal death in some patients. Anticoagulation was even found to be a significant (univariate) risk factor of maternal mortality in patients with SVPH. In contrast, judicious use of antithrombotic drugs contributed to survival in a number of patients with Eisenmenger's syndrome, PPH and SVPH (41,42,52,64,65,73,75,80,99).

Timing of maternal death. The first month after delivery represents the period of highest risk for patients with PVD (Fig. 1). Longitudinal studies in healthy parturients found the lowest myocardial contractility at delivery and immediately postpartum and slow cardiovascular recovery over the next 3 months (108,109). The speculative explanations for predominant postpartal fatalities in PVD include an increased tendency toward thromboembolism, an exaggerated pulmonary vascular reactivity and/or a mismatch between declined myocardial contractility and a too sudden decrease in blood volume after delivery.

Neonatal outcome. Only cases of late pregnancy were reviewed, and no conclusions can be drawn about the overall fetal outcome, particularly of early pregnancy, in women with PVD. A neonatal survival rate of nearly 90% was surprisingly high. If previous pregnancies are considered, the rate is still 82% in the group with Eisenmenger's syndrome. The neonatal outcome depended on maternal tolerance of late pregnancy and the presence of congenital anomalies, and not on the type of PVD. Although these survival data are encouraging, the differences in maternal and neonatal outcome implicate a "conflict of interest" between the pregnant patient with PVD and the fetus.

Study limitations. The published data offered only a limited amount and quality of information. A larger number of prospectively studied patients would provide a precise pattern of hemodynamic changes, differentiate the risks of pregnancy and eventually provide an optimal plan of peripartal management. However, the incidence of PVD in late pregnancy is relatively low. Our systematic search revealed 125 cases reported in the last two decades, and only a few reports provided detailed information on a series of patients. Some reports, perhaps including many patients, remain unpublished, and it is speculative whether the bias to report a successful outcome is balanced by the negative selection of the most severe cases of PVD. The review is a quantitative summary of experiences from various institutions and countries, and the results should be seen as best available global estimates of the management and outcome of late pregnancy in women with PVD.

Conclusions. The outcome of pregnant women with Eisenmenger's syndrome in the last two decades has not changed compared with the period before 1978. Maternal mortality rates of 30% to 36% were almost identical in patients with PPH and Eisenmenger's syndrome, whereas the rate was relevantly higher (>50%) in those with SVPH. Late diagnosis and late hospital admission were strong independent risk factors of maternal mortality. Operative delivery, severity of pulmonary hypertension, number of previous pregnancies and deliveries and indiscriminate use of anticoagulant drugs must be considered as contributing risk factors. Almost all maternal deaths occurred early after delivery; thus, intensive medical therapy and care should be employed in the highly vulnerable postpartal period in women with PVD.

References

1. Clark SL. Cardiac disease in pregnancy. In: Reece EA, Hobbins JC, Mahoney MJ, Petrie RH, editors. Medicine of the Fetus and Mother. Philadelphia: J.B. Lippincott, 1992:943–54.
2. James KB. Heart disease arising during pregnancy. In: Douglas PS, editor. Cardiovascular Health and Disease in Women. Philadelphia: W.B. Saunders, 1993:337–59.
3. Weiss BM, Atanassoff PG. Cyanotic congenital heart disease and pregnancy: natural selection, pulmonary hypertension, and anesthesia. J Clin Anesth 1993;5:332–41.
4. Perloff JK. The Clinical Recognition of Congenital Heart Disease. Philadelphia: W.B. Saunders, 1994:198–202, 273–7.
5. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med 1991;115:343–9.
6. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. J Heart Lung Transplant 1996;15:100–5.
7. Gleicher N, Midwall J, Hochberger D, Jaffin H. Eisenmenger's syndrome and pregnancy. Obstet Gynecol Surv 1979;34:721–41.
8. Maarek-Charbit M, Corone P. Eisenmenger syndrome and pregnancy. Arch Mal Cœur 1986;5:733–40.
9. Rubin LJ. ACCP consensus statement: primary pulmonary hypertension. Chest 1993;104:236–50.
10. Atanassoff PG, Schmid ER, Jenni R, Arbenz U, Alon E, Pasch T. Epidural anesthesia for cesarean section in a patient with pulmonary atresia and ventricular septal defect. J Clin Anesth 1991;3:399–402.
11. Atanassoff PG, Alon E, Schmid ER, Pasch T. Epidural anesthesia for cesarean section in a patient with severe pulmonary hypertension. Acta Anaesthesiol Scand 1990;34:75–7.
12. Pollack KL, Chestnut DH, Wenstrom KD. Anesthetic management of a parturient with Eisenmenger's syndrome. Anesth Analg 1990;70:212–5.
13. Heytens L, Alexander JP. Maternal and neonatal death associated with Eisenmenger's syndrome. Acta Anaesth Belg 1986;37:45–51.
14. Robinson PN, Macleod KGA. Location for delivery in a patient with Eisenmenger's syndrome [letter]. Anaesthesia 1986;41:883–4.
15. Garber SZ, Choi HJ, Tremper KK, Fujita RA. Use of a pulse oximeter in the anesthetic management of a pregnant patient with Eisenmenger's syndrome. Anesth Rev 1988;15:59–63.
16. Lawlor MC, Johnson C. Anesthetic management of emergency cesarean delivery in a patient with Noonan and Eisenmenger syndromes. Reg Anesth 1994;19:142–5.
17. Wilton NCT, Traber KB, Deschner LS. Anaesthetic management for caesarean section in a patient with uncorrected truncus arteriosus. Br J Anaesth 1989;62:434–8.
18. McMurray TJ, Kenny NT. Extradural anaesthesia in parturients with severe cardiovascular disease: two case reports. Anaesthesia 1982;37:442–5.
19. Lui P, Silvay G, Palop R, Stark DCC, Sonnenklar N, Jaffin H. Eisenmenger syndrome—anesthetic management for labor and delivery: a case report. Mt Sinai J Med 1978;45:411–4.
20. Tibaldi G, Marchi L, Huscher M, Forlini G. Anesthesia for a cesarean

section in a woman with Eisenmenger's disease. Minerva Ginecol 1988;40: 145–6.
21. Alahuhta S, Jouppila P. Pregnancy after cardiac surgery in patients with secondary pulmonary hypertension due to a ventricular septal defect. Acta Obstet Gynecol Scand 1994;73:836–8.
22. Jackson GM, Dildy GA, Varner MW, Clark SL. Severe pulmonary hypertension in pregnancy following successful repair of ventricular septal defect in childhood. Obstet Gynecol 1993;82:680–2.
23. Green NJ, Rollason TP. Pulmonary artery rupture in pregnancy complicating patent ductus arteriosus. Br Heart J 1992;68:616–8.
24. Stoddart P, O'Sullivan G. Eisenmenger's syndrome in pregnancy: a case report and review. Int J Obstet Anesth 1993;2:159–68.
25. Gilman DH. Caesarean section in undiagnosed Eisenmenger's syndrome: report of a patient with a fatal outcome. Anaesthesia 1991;46:371–3.
26. Rao UR, Nalini V. Eisenmenger's syndrome complicating pregnancy. J Indian Med Assoc 1989;87:266–8.
27. Jeyamalar R, Sivanesaratnam V, Kuppuvelumani P. Eisenmenger syndrome in pregnancy. Aust N Z J Obstet Gynaecol 1992;32:275–7.
28. Bitsch M, Johansen C, Wennevold A, Osler M. Eisenmenger's syndrome and pregnancy. Eur J Obstet Gynecol Reprod Biol 1988;28:69–74.
29. Rosenberg B, Simon K, Peretz BA, Roguin N, Birkhahn HJ. Eisenmenger's syndrome in pregnancy: controlled segmental epidural block for caesarean section. Reg Anaesth 1984;7:131–3.
30. Spinnato JA, Kraynack BJ, Cooper MW. Eisenmenger's syndrome in pregnancy: epidural anesthesia for elective cesarean section. N Engl J Med 1981;304:1215–7.
31. Mukhtar AI, Halliday HL. Eisenmenger syndrome in pregnancy: a possible cause of neonatal polycythemia and persistent fetal circulation. Obstet Gynecol 1982;60:651–2.
32. Lieber S, Dewilde P, Huyghens L, Traey E, Gepts E. Eisenmenger's syndrome and pregnancy. Acta Cardiol 1985;40:421–4.
33. Sinnenberg RJ Jr. Pulmonary hypertension in pregnancy. South Med J 1980;73:1529–31.
34. Russo R, Bortolotti U, Grella P, Terribile V, Schivazappa L. Eisenmenger syndrome and pregnancy. Minerva Cardioangiol 1980;28:711–5.
35. Blake P, McDonald D, Blake S. Pregnancy in patients with Eisenmenger's syndrome. Irish Med J 1983;76:308–9.
36. Pirlo A, Herren AL. Eisenmenger's syndrome and pregnancy: a case report and review of the literature. Anesth Rev 1979;6:9–16.
37. Jewett JF. Pulmonary hypertension and pre-eclampsia [letter]. N Engl J Med 1979;301:1063–4.
38. Kahn ML. Eisenmenger's syndrome in pregnancy [letter]. N Engl J Med 1993;329:887.
39. Huyghe de Mahence A, Andre-Fouet X, Bernet D, et al. Eisenmenger's syndrome and pregnancy: report of two cases of spontaneous delivery, one of which was fatal. Ann Cardiol Angeiol (Paris) 1985;34:547–9.
40. Antoine JM, Bonnardot JP, Vitoux B, Salat-Baroux J. Eisenmenger syndrome and pregnancy: one case. J Gynecol Obstet Biol Reprod 1991;20: 79–82.
41. Avila WS, Grinberg M, Snitcowsky R, et al. Maternal and fetal outcome in pregnant women with Eisenmenger's syndrome. Eur Heart J 1995;16: 460–4.
42. Smedstad K, Cramb R, Morison DH. Pulmonary hypertension and pregnancy: a series of eight cases. Can J Anaesth 1994;41:502–12.
43. Gummerus M, Laasonen H. Eisenmenger complex and pregnancy. Ann Chir Gynaecol 1981;70:339–41.
44. Sulovic V, Radunovic N, Krstic N. Eisenmenger's syndrome and pregnancy. Jugosl Ginekol Opstet 1983;23:131–2.
45. Schwalbe SS, Deshmukh SM, Marx GF. Use of pulmonary artery catheterization in parturients with Eisenmenger's syndrome [letter]. Anesth Analg 1990;71:442–3.
46. Oakley CM, Nihoyannopoulos P. Peripartum cardiomyopathy with recovery in a patient with coincidental Eisenmenger ventricular septal defect. Br Heart J 1992;67:190–2.
47. Hankins GDV, Brekken AL, Davies LM. Maternal death secondary to a dissecting aneurysm of the pulmonary artery. Obstet Gynecol 1985;65:45S–8S.
48. Midwall J, Jaffin H, Herman MV, Kupersmith J. Shunt flow and pulmonary hemodynamics during labor and delivery in the Eisenmenger syndrome. Am J Cardiol 1978;42:299–303.
49. Ogura M, Suzukawa M, Tagami M, et al. High-dose fentanyl anesthesia in a pregnant patient with Eisenmenger's syndrome. Masui 1985;34:241–6.
50. Kubo N, Yokoyama K. Lumbar epidural and caudal anesthesia for vaginal delivery in Eisenmenger's syndrome. Masui 1981;30:1388–95.
51. Camba Rodriguez MA, Yanez Gonzalez AM, Gonzalez Ruiz F. Epidural anaesthesia for cesarean section in a patient with Eisenmenger's syndrome. Rev Esp Anestesiol Reanim 1989;36:45–7.
52. Buckshee K, Biswas A, Mittal S, Agarwal N. Eisenmenger's syndrome with pregnancy: a rare obstetrical problem with successful outcome. Asia Oceania J Obstet Gynaecol 1988;14:323–5.
53. Patton DE, Lee W, Cotton DB, et al. Cyanotic maternal heart disease in pregnancy. Obstet Gynecol Surv 1990;45:594–600.
54. Devitt JH, Noble WH, Byrick RJ. A Swan-Ganz catheter related complication in a patient with Eisenmenger's syndrome. Anesthesiology 1982;57: 335–7.
55. Furuya H, Okumura F, Ishida T, Chiba Y. General anesthesia for a cesarean section in a patient with Eisenmenger's syndrome. Masui 1983; 32:1269–73.
56. Muller BJ, Steude G. General anesthesia administered to a patient with Eisenmenger's syndrome undergoing cesarean section. Anesth Rev 1982; 9:32–5.
57. Johnston TA, De Bono D. Single ventricle and pulmonary hypertension: a successful pregnancy: case report. Br J Obstet Gynaecol 1989;96:731–4.
58. Ross-Ascuitto N, Ascuitto RJ, Darnell J. A pregnant women with moderate pulmonary hypertension. Pediatr Cardiol 1995;16:31–2.
59. Tampakoudis P, Grimbizis G, Chatzinicolaou K, Mantalenakis S. Successful pregnancy in a patient with severe pulmonary hypertension. Gynecol Obstet Invest 1996;42:63–5.
60. Hossack KF, Tewksbury JC, Reid LM. Successful repair of an atrial septal defect associated with right to left shunting. Br Heart J 1989;62:69–73.
61. Bitsch M, Johansen C, Wennevold A, Osler M. Maternal heart disease: a survey of a decade in a Danish university hospital. Acta Obstet Gynecol Scand 1989;68:119–24.
62. Slomka F, Salmeron S, Zetlaoui P, Cohen H, Simonneau G, Samii K. Primary pulmonary hypertension and pregnancy: anesthetic management for delivery. Anesthesiology 1988;69:959–61.
63. Power KJ, Avery AF. Extradural analgesia in the intrapartum management of a patient with pulmonary hypertension. Br J Anaesth 1989;63:116–20.
64. Roessler P, Lambert TF. Anaesthesia for caesarean section in the presence of primary pulmonary hypertension. Anaesth Intensive Care 1986;14:317–20.
65. Kasai H, Gohda Y, Sasaki K, Kemmotsu O. Anesthetic management of caesarean section in a patient with primary pulmonary hypertension. Masui 1988;37:476–82.
66. Pfisterer J, Runge HM, Kommoss F, Herbst EW, Hillemanns HG. Primary pulmonary hypertension and pregnancy. Geburts Frauenheilk 1991;51: 236–8.
67. Dawkins KD, Burke CM, Billingham ME, Jamieson SW. Primary pulmonary hypertension and pregnancy. Chest 1986;89:383–8.
68. Tsou E, Waldhorn RE, Kerwin DM, Katz S, Patterson JA. Pulmonary venoocclusive disease in pregnancy. Obstet Gynecol 1984;64:281–4.
69. Nelson DM, Main E, Crafford W, Ahumada GG. Peripartum heart failure due to primaty pulmonary hypertension. Obstet Gynecol 1983;62:58S–63S.
70. Takeuchi T, Nishii O, Okamura T, Yaginuma T. Primary pulmonary hypertension in pregnancy. Int J Gynecol Obstet 1988;26:145–50.
71. Kiss H, Egarter C, Asseryanis E, Putz D, Kneussel M. Primary pulmonary hypertension in pregnancy: a case report. Am J Obstet Gynecol 1995;172: 1052–4.
72. Martinez JM, Comas C, Sala X, Gratacos E, Torres PJ, Fortuny A. Maternal primary pulmonary hypertension associated with pregnancy. Eur J Obstet Gynecol Reprod Biol 1994;54:143–7.
73. Nootens M, Rich S. Successful management of labor and delivery in primary pulmonary hypertension. Am J Cardiol 1993;71:1124–5.
74. Feijen HWH, Hein PR, van Lakwijk-Vondrovicova EL, Nijhuis GMM. Primary pulmonary hypertension and pregnancy. Eur J Obstet Gynecol Reprod Biol 1983;15:159–64.
75. Nakamura M, Kobayashi T, Mochizuki N, et al. Peripartum deterioration of hemodynamics in a patient with primary pulmonary hypertension. Kokyu To Junkan 1987;35:1005–10.
76. Slavin AG. Importance of hyperbaric oxygenation for a favorable outcome

of labor in primary pulmonary hypertension patients. Vopr Okhr Materin Det 1979;24:64–6.
77. Medvedev BI, Briukhina EV, Smirnova ZA. Primary pulmonary hypertension and pregnancy. Akush Ginekol Mosk 1986;68–9.
78. Breen TW, Janzen JA. Pulmonary hypertension and cardiomyopathy: anaesthetic management for caesarean section. Can J Anaesth 1991;38: 895–9.
79. Khan MJ, Bhatt SB, Kryc JJ. Anesthetic considerations for parturients with primary pulmonary hypertension: review of the literature and clinical presentation. Int J Obstet Anesth 1996;5:36–42.
80. Rocha MP, Guntupalli KK, Moise KJ Jr, Lockett LD, Khawli F, Rokey R. Massive hemoptysis in Takayasu's arteritis during pregnancy. Chest 1994; 106:1619–22.
81. Roberts NV, Keast PJ. Pulmonary hypertension and pregnancy—a lethal combination. Anaesth Intensive Care 1990;18:366–74.
82. Kuroiwa M, Meno H, Higashi H, Hamanaka N, Takita J. A case report of primary pulmonary hypertension: congestive heart failure induced by pregnancy and delivery. Kokyu To Junkan 1992;40:691–4.
83. Rubin LA, Geran A, Rose TH, Cohen H. A fatal pulmonary complication of lupus in pregnancy. Arthritis Rheum 1995;38:710–4.
84. Watanabe R, Tatsumi K, Uchiyama T, et al. Puerperal secondary pulmonary hypertension in a patient with mixed connective tissue disease. Nippon Kyobu Shikkan Gakkai Zasshi 1995;33:883–7.
85. Van Enk A, Visschers G, Jansen W, Statius Van Eps LW. Maternal death due to sickle sell chronic lung disease. Br J Obstet Gynaecol 1992;99:162–3.
86. Hubscher O, Eimon A, Elsner B, Arana RM. Fatal post-partum pulmonary vasculitis in systemic lupus erythematosus. Clin Rheumatol 1984;3:547–50.
87. Ray J, Sermer M. Systemic lupus erythematosus and pulmonary hypertension during pregnancy: report of a case fatality. Can J Cardiol 1996;12: 753–6.
88. Thompson J, Conklin KA. Anesthetic management of a pregnant patient with scleroderma. Anesthesiology 1983;59:69–71.
89. Younker D, Harrison B. Scleroderma and pregnancy: anaesthetic considerations. Br J Anaesth 1985;57:1136–9.
90. Baethge BA, Wolf RE. Successful pregnancy with scleroderma renal disease and pulmonary hypertension in a patient using angiotensin converting enzyme inhibitors. Ann Rheum Dis 1989;48:776–8.
91. Abboud TK, Raya J, Noueihed R, Daniel J. Intrathecal morphine for relief of labor pain in a parturient with severe pulmonary hypertension. Anesthesiology 1983;59:477–9.
92. Bredgaard Sorensen M, Korshin JD, Fernandes A, Secher O. The use of epidural analgesia for delivery in a patient with pulmonary hypertension. Acta Anaesth Scand 1982;26:180–2.
93. Sala-Blanch X, Fabregas N, Martinez JM, Plaza A. Primary pulmonary hypertension in a gravida with the human immunodeficiency virus [letter]. Med Clin (Barc) 1994;102:117–8.
94. Lundquest DE, Young WK, Edland JF. Maternal death associated with intravenous methylphenidate (Ritalin) and pentazocine (Talwin) abuse. J Forensic Sci 1987;32:798–801.
95. Atanassoff PG, Weiss BM, Schmid ER, Tornic M. Pulmonary hypertension and dexfenfluramine [letter]. Lancet 1992;339:436.
96. Robinson DE, Leicht CH. Epidural analgesia with low-dose bupivacaine and fentanyl for labor and delivery in a parturient with severe pulmonary hypertension. Anesthesiology 1988;68:285–8.
97. Sugioka J, Nakajima T, Ohsumi H, Kuro M, Sasako Y. Anesthetic management using percutaneous cardiopulmonary support for cesarean section in a patient with severe pulmonary hypertension. Masui 1995;44: 574–8.
98. Dubois RS, Slovis TL, Tolia V, Pensler L. Chronic active hepatitis and pregnancy: a report of two cases in adolescence. Am J Gastroenterol 1982;77:649–51.
99. Leduc L, Kirshon B, Diaz SF, Cotton DB. Intrathecal morphine analgesia and low-dose dopamine for oliguria in severe maternal pulmonary hypertension: a case report. J Reprod Med 1990;35:727–9.
100. Togo T, Sugishita Y, Tamura T, et al. Uneventful pregnancy and delivery in a case of multiple peripheral pulmonary stenoses. Acta Cardiol 1983;38: 143–51.
101. Landsberger EJ, Grossman JH III. Muliple peripheral pulmonic stenosis in pregnancy. Am J Obstet Gynecol 1986;154:152–3.
102. Presbitero P, Rabajoli F, Somerville J. Pregnancy in patients with congenital heart disease. Schweiz Med Wochenschr 1995;125:311–5.
103. Saha A, Balakrishnan KG, Jaiswal PK, et al. Prognosis for patients with Eisenmenger syndrome of various aetiology. Int J Cardiol 1994;45:199–207.
104. Meyer NL, Mercer B, Khoury A, Sibai B. Pregnancy complicated by cardiac disease: maternal and perinatal outcome. J Maternal Fetal Med 1994;3: 31–6.
105. Sitbon O, Brenot F, Denjean A, et al. Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension: a dose-response study and comparison with prostacyclin. Am J Respir Crit Care Med 1995;151:384–9.
106. Shapiro SM, Oudiz RJ, Cao T, et al. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. J Am Coll Cardiol 1997;30:343–9.
107. Oakley CM. Pregnancy and congenital heart disease. Heart 1997;78:12–4.
108. Mone SM, Sanders S, Colan SD. Control mechanisms for physiological hypertrophy of pregnancy. Circulation 1996;94:667–72.
109. Capeless EL, Clapp JF. When do cardiovascular parameters return to their preconception values? Am J Obstet Gynecol 1991;165:883–6.