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REVIEW

Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension?

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Pregnancy in women with pulmonary arterial hypertension (PAH) is considered to be associated with prohibitive maternal mortality. During the past decade, new advanced therapies for PAH have emerged and progress in high-risk pregnancy management has been made. We examined whether these changes have improved outcomes in parturients with PAH. A systematic review of all cases of parturients with idiopathic pulmonary hypertension (iPAH), congenital heart disease associated with PAH (CHD-PAH), or PAH of other aetiology (oPH) published in the past decade (1997–2007) was performed. Outcome data from this study were then compared with relevant data published between 1978 and 1996. Forty-eight case reports or case series met the inclusion criteria, totalling 73 parturients with PAH. Seventy-two per cent of patients with iPAH were receiving advanced therapies, compared with 52% of CHD-PAH and 47% of oPH. Although a publication bias cannot be excluded, overall maternal mortality was significantly lower compared with previous era (25 vs. 38%, $P = 0.047$) and was 17% in iPAH, 28% in CHD-PAH, and 33% in oPH. Seventy-eight per cent of deaths occurred within the first month after delivery. Primigravidae and parturients who received general anaesthesia were at higher risk of death (OR 3.70, 95% CI 1.15–12.5, $P = 0.03$ and OR 4.37, 95% CI 1.28–16.50, $P = 0.02$, respectively). Maternal mortality in parturients with PAH remains prohibitively high, despite lower death rates than previous decades. Early advice on pregnancy risks, including contraception, remains paramount. Women with PAH who become pregnant warrant a multidisciplinary approach with consideration of advanced therapies.

Keywords Pregnancy • Pulmonary hypertension • Congenital • Eisenmenger

Introduction

Pregnancy in women with pulmonary arterial hypertension (PAH), including idiopathic (iPAH), in association with congenital heart disease (CHD-PAH) or PAH owing to other causes (oPH), is known to be associated with a high maternal mortality, estimated between 30 and 56%.[1] The physiological changes that occur during pregnancy and the peri-partum seem to be poorly tolerated in these patients. Recent practice guidelines from the European Society of Cardiology and the American College of Cardiology/American Heart Association strongly discourage pregnancy in these patients and advise termination should pregnancy occur.[2]

During the past decade or so, new advanced therapies for the treatment of PAH have been developed, improving overall quality of life and prognosis for these patients.[3,4] Moreover and perhaps more importantly, the management of high-risk pregnancies has improved owing to earlier recognition of the underlying disease, improved understanding of cardiopulmonary pathophysiology, better obstetric/anaesthetic management, and the introduction of a multidisciplinary approach.[5] Whether these changes have translated into a reduction in maternal mortality remains unknown.

We examined herewith whether the contemporary approach to pregnancy and PAH as mentioned above has had an impact on outcome.

Methods

Material

A systematic review of all published reports of pregnancies in women with PAH was performed. The database of the National Library of Medicine (MEDLINE) was interrogated for publications in any language, between January 1997 and September 2007. Articles in

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non-English language were included when an English translation of the paper was available. Keywords used were 'pregnancy', 'pregnant', 'pulmonary hypertension', 'Eisenmenger', 'Eisenmenger's syndrome', 'primary or idiopathic pulmonary hypertension', 'pulmonary vascular disease', and 'congenital heart disease'. Cases of PAH secondary to chronic lung disease or acquired heart disease were excluded. Cases of pregnancy termination and spontaneous abortion before 22 weeks of gestation were also excluded, as the focus of the present study was to evaluate how women with PAH and their babies cope with the haemodynamic burden of pregnancy beyond the second trimester and delivery. Moreover, this approach allowed us to perform a comparative analysis, with the data from the study by Weiss *et al.*,[1] reporting on outcome of late pregnancy (beyond 22 weeks) in patients with PAH between 1978 and 1996. When no specific cause of PAH was identified, the case was classified as iPAH. Patients with congenital heart disease associated with PAH were included in the CHD-PAH group (including Eisenmenger syndrome). Cases were classified as oPH when PAH was secondary to connective tissue disease, systemic vasculitis, medication-induced PAH, pulmonary thrombo-embolism, HIV, or chronic hepatitis.

Statistical analysis

Statistical analysis was performed using R version 2.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Patient characteristics, peripartum management, and outcome of pregnancies were presented separately for each group (iPAH, CHD-PAH, and oPH). Numerical values were presented as median (range) and categorical variables as number (percentage of total available) per group. Maternal mortality was presented as per cent of total within each PAH group, with 95% CI. Univariable logistic regression was used to identify predictors of maternal death between demographic and clinical variables, including age, gravida (number of previous pregnancies), para (number of living children), timing of diagnosis (before or during pregnancy), NYHA functional class during pregnancy, mean pulmonary artery pressure (MAP), week of pregnancy at hospital admission and at delivery, mode of delivery (vaginal vs. caesarean), use of invasive monitoring, type of anaesthesia (general or regional), use of anticoagulation, and use of advanced therapy [nitric oxide (NO), prostacyclin analogues, bosentan or sildenafil]. No multivariable analyses were performed owing to the relatively low number of adverse events. Mean pulmonary artery pressure, when not reported, was approximated using the following equation: MAP = diastolic PAP + 1/3 (systolic PAP − diastolic PAP), or derived from echocardiographic data using the Bernoulli formula (MAP = systolic PAP estimated by echocardiogram/4 × 2.4). Comparison between outcomes reported in this study and published data from 1978 to 1996[1] was performed using the χ^2 test. All *P*-values were two-sided and a *P*-value of <0.05 was pre-specified as indicative of statistical significance.

Results

Patient population

Our search results and study selection process are presented in *Figure 1*. Forty-seven case reports or case series met the inclusion criteria, totalling 73 parturients with PAH.[5–52] Characteristics of the patients from each group are presented in *Table 1*, whereas specific defect type of parturients with CHD-PAH is shown in *Figure 2*. Underlying diagnosis for oPH patients were pulmonary vasculitis related to systemic lupus erythematosus ($n = 4$), progressive systemic sclerosis ($n = 1$) or mixed connective tissue disease ($n = 1$), antiphospholipid syndrome with previous pulmonary embolism ($n = 2$), chronic pulmonary thrombo-embolism ($n = 3$), appetite suppressant drugs ($n = 1$), HIV ($n = 2$), and hepatitis ($n = 1$). The overall median age was 29 (range 21–39) years. CHD-PAH patients had the lowest resting arterial oxygen saturations (median 83 vs. 92% in the remainder, $P = 0.01$) and the highest haemoglobin concentration (median 16.0 vs. 11.4 g/dL, $P = 0.003$). Overall, MAP was 50 mmHg (28–120 mmHg), with no differences between subgroups. Sixty-one per cent of parturients were classified as NYHA functional class III or IV during pregnancy.

Management and outcomes

Idiopathic pulmonary arterial hypertension

Advanced therapies for PAH were used during pregnancy, labour, or delivery in 21 (72%) iPAH patients (*Table 1*); 2 of 29 (7%) died during pregnancy, whereas 3 (10%) died in the post-partum period (days 7, 14, and 90). Severe therapy-resistant right heart failure,

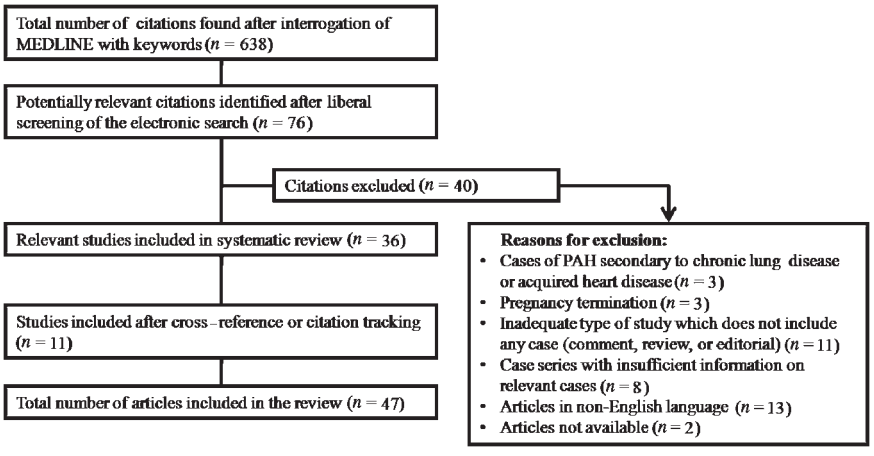

Figure 1 Search results and study selection process.

Table 1 Baseline characteristics, management, and outcome of parturients with pulmonary arterial hypertension

	iPAH ($n = 29$)	CHD-PAH ($n = 29$)	oPH ($n = 15$)
Characteristics			
Age (years)	29 (21–39)	27 (21–38)	30 (23–41)
Gravida	2 (1–4)	2 (1–5)	2 (1–9)
Para	1 (0–3)	0 (0–2)	0 (0–7)
Diagnosis made			
Before pregnancy	13 (45%)	22 (76%)	12 (80%)
During pregnancy	16 (55%)	7 (24%)	3 (20%)
NYHA class during pregnancy	4 (1–4)	3 (1–4)	2 (2–4)
Sa_{O_2} during pregnancy (%)	93 (88–96)	83 (69–96)	Not reported
Hb during pregnancy (g/dL)	11.4 (11.4–12.6)	16 (14.1–19.5)	10 (8–12)
PAP, systolic (mmHg)	78 (38–130)	85 (44–130)	73 (48–100)
PAP, diastolic (mmHg)	37 (14–62)	31 (20–42)	26 (18–40)
PAP, mean (mmHg)	51 (30–120)	50 (28–78)	46 (24–75)
Management			
Hospital admission, weeks of pregnancy	28 (12–37)	32 (17–40)	28 (23–35)
Delivery, weeks of pregnancy	34 (25–39)	34 (26–40)	32 (26–36)
Mode of delivery			
Vaginal	8 (30%)[a]	8 (28%)	1 (7%)[b]
Caesarean section	19 (70%)	21 (72%)	13 (93%)
Monitoring during peri-partum			
Radial artery and/or CVP catheter	9 (31%)	11 (38%)	5 (33%)
Pulmonary artery catheter	22 (76%)	9 (31%)	9 (60%)
Anaesthesia			
Regional	18 (67%)[a]	17 (59%)	4 (28%)[b]
General anaesthesia	8 (29%)	9 (31%)	6 (43%)
Not reported	1 (4%)	3 (10%)	4 (29%)
Antithrombotic therapy			
During pregnancy	15 (52%)	7 (24%)	7 (47%)
Post-partum	11 (41%)[a]	9 (31%)	5 (36%)[b]
Advanced therapy for PAH			
Nitric oxide	7 (24%)	7 (24%)	5 (33%)
Prostacyclin analogues	18 (62%)	9 (31%)	3 (20%)
Bosentan	1 (3%)[c]	1 (3%)	0 (0%)
Sildenafil	1 (3%)[c]	4 (14%)	0 (0%)
None	8 (28%)	14 (48%)	8 (53%)
Calcium channel blockers	9 (31%)	6 (21%)	4 (27%)
Outcomes			
Follow-up, days post-partum	310 ($\pm$229)	243 ($\pm$147)	255 ($\pm$196)
Maternal death	5 (17%)	8 (28%)	5 (33%)
During pregnancy	2 (7%)	0 (0%)	1 (7%)
Weeks of pregnancy	12 and 28	—	23
Post-partum ($\leq$90 days)	3 (10%)	8 (28%)	4 (26%)
Days post-partum	14 (7–90)	6 (0–24)	1.5 (1–21)
Other complications reported[d]			
Pulmonary hypertensive crisis	3 (10%)	2 (7%)	0 (0%)
Pulmonary thrombo-embolism	0 (0%)	4 (14%)	3 (20%)
RV failure	9 (31%)	9 (31%)	4 (27%)
Bleeding or fall in Hb + transfusion	3 (10%)	11 (38%)	4 (27%)
Premature delivery[e]	23 (85%)[a]	25 (86%)	14 (100%)[b]

Continued

Table 1 *Continued*

	iPAH ($n = 29$)	CHD-PAH ($n = 29$)	oPH ($n = 15$)
Neonatal or foetal death	3 (10%)	2 (7%)	2 (13%)
Intrauterine growth retardation reported	1 (3%)	7 (24%)	5 (33%)

Hb, haemoglobin; NYHA, New York Heart Association Classification ($n = 44$); PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure during pregnancy; Sa_{O_2}, arterial oxygen saturation ($n = 24$).
[a]Two patients died before delivery.
[b]One patient died before delivery.
[c]Given post-partum.
[d]Including patients who did not die.
[e]Defined as delivery that occurs before 37 completed weeks of gestation.

circulatory collapse, and pulmonary hypertension crisis were the reported causes of death (*Table 2*). One late maternal death was reported 19 months post-delivery. However, only 13 (54%) of the 24 patients who survived had more than 1 year of follow-up.

There were three (10%) foetal deaths; two secondary to maternal death and one was a twin who died *in utero* at 17 weeks of gestation. All live-born infants survived.

Congenital heart disease-associated pulmonary arterial hypertension

Fifteen (52%) CHD-PAH patients received advanced PAH therapy (*Table 1*). Eight (28%) patients died, all after delivery (median time to death 6 days post-partum, range 0–24); severe right heart failure was reported in six of them. Other causes of death included pulmonary thrombo-embolism, sudden cardiac death, pulmonary hypertension crisis, and bacterial endocarditis (*Table 2*). One late maternal death was reported 14 months following delivery, owing to severe right heart failure.

There were two (7%) foetal/neonatal deaths. One was a stillbirth at 36 weeks of gestation. The second was a baby delivered prematurely at 30 weeks of pregnancy, who died at 26 days of life because of sepsis. Intrauterine growth restriction was reported in seven (24%) newborns.

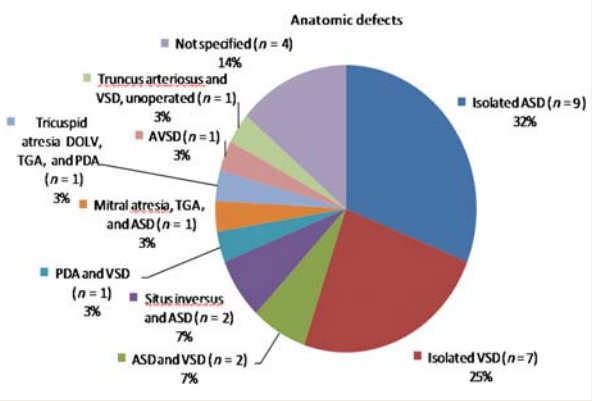

Figure 2 Specific cardiac anatomy in parturients with congenital heart disease-associated pulmonary arterial hypertension ($n = 29$). ASD, atrial septal defect; AVSD, atrioventricular septal defect; DOLV, double outlet left ventricle; PDA, patent ductus arteriosus; TGA, transposition of great arteries.

Other pulmonary arterial hypertension

Seven (47%) oPH patients received advanced PAH therapy (*Table 1*). One patient died during pregnancy, whereas four died in the early post-partum [days 1 ($n = 2$), 2, and 21]. Causes of death were severe right heart failure and pulmonary thrombo-embolism (*Table 2*). The underlying causes of PAH in the patients who died were systemic lupus erythematosus ($n = 1$), chronic pulmonary thrombo-embolism ($n = 1$), appetite suppressant drugs ($n = 1$), antiphospholipid syndrome with previous pulmonary embolism, chronic active hepatitis ($n = 1$) and autoimmune hepatitis ($n = 1$). One patient with progressive systemic sclerosis died 24 months post-partum secondary to fulminant respiratory failure with lung infection.

One foetal death was due to maternal death at 23 weeks of pregnancy, whereas a prematurely delivered infant (32 weeks) died in the early neonatal period. Intrauterine growth restriction was present in five (33%) foetuses.

Maternal death and predictors of outcome

Overall, maternal mortality for parturients with PAH was lower in the last decade compared with previous era ($P = 0.047$, *Figure 3*). Mortality decreased substantially in all three subgroups (from 30 to 17% in iPAH, 36 to 28% in CHD-PAH, and 56 to 33% in oPH), although not reaching statistical significance. Furthermore, no significant differences in mortality were seen between the three subgroups over the last decade ($P = 0.41$). Patients receiving general anaesthesia were four times more likely to die, compared with patients receiving regional anaesthesia (OR 4.37, 95% CI 1.28–16.5, $P = 0.02$). Primigravidae were at higher mortality risk compared with parturients with previous pregnancies (OR 3.70, 95% CI 1.15–12.5, $P = 0.03$). No other clinical variables, including advanced PAH therapies related to maternal mortality.

Other noticeable differences with previous decades

Only 17 (24%) patients from this study had vaginal delivery, lower than during the previous era (53%, $P = 0.0001$).[1] Moreover, the proportion of premature deliveries in the current study was higher (85 vs. 59% in iPAH and 86 vs. 53% in CHD-PAH).[1]

Table 2 Cases of maternal death

Reference	Anticoagulation	Advanced PAH therapies	Other treatment	Type of delivery	Timing of death	Cause of death
iPAH						
Bonnin *et al.*[10]	Not reported	None	None	Died before delivery	12th week of pregnancy	Circulatory collapse
Easterling *et al.*[21]	Heparin	Prostacyclin (initiated after decompensation)	Dobutamine, bicarbonate	Died before delivery	28th week of pregnancy	Severe RV failure
Takeuchi *et al.*[22]	Prophylactic heparin (initiated at 27 weeks of gestation	None	Nifedipine, nitrates, spironolactone, prostaglandine E1, and human ANP	Caesarean section	7 days post-partum	Hypotension, severe RV failure, and pulmonary hypertensive crisis
Monnery *et al.*[15]	Heparin before and after delivery	Prostacyclin, NO	Prostaglandin I2, nifedipine, aspirin, corticosteroids	Caesarean section	14 days post-partum	Severe RV failure
Bonnin *et al.*[10]	Unknown	Prostacyclin	Furosemide, dobutamine	Vaginal	90 days post-partum	Circulatory collapse
CHD-PAH						
Sung *et al.*[41]	Not reported	None	Diuretics, nifedipine, dopamine, nitroglycerine, ephedrine, epinephrine	Caesarean section	12 h post-partum	Severe RV failure; no bleeding but needed packed erythrocytes + platelets
Phupong *et al.*[33]	None	None	None	Caesarean section	2 days post-partum	Cardiac arrest
Hussain *et al.*[27]	Anticoagulation 36 h post-partum (suspicion of PE)	None	Hydralazine, furosemide	Caesarean section	3 days post-partum	PE; no overt bleeding but Hb fell to 10.0 g/dL and required packed erythrocytes
Ding *et al.*[32]	Not reported	None	Mg, inotropic agents gabexate mesilate, and vancomycine	Caesarean section	5 days post-partum	Endocarditis with PE and RV failure
Goodwin *et al.*[38]	None during pregnancy; iv/sc heparin after delivery	NO and prostacyclin (initiated after decompensation)	None	Vaginal	6 days post-partum	Pulmonary thrombo-embolism and RV failure
Bonnin *et al.*[10]	Not reported	None	None	Caesarean section	7 days post-partum	Severe RV failure
Lust *et al.*[40]	Heparin before and after delivery	NO, prostacyclin	Nifedipine, aminophylline, norepinephrine	Vaginal	21 days post-partum	Pulmonary hypertension crisis and RV failure; heavy vaginal bleeding
Kansaria and Salvi.[36]	Not reported	None	Digoxin, hydrochlorothiazide, and dopamine	Vaginal	24 days post-partum	Severe RV failure; large episiotomy haematoma

oPH						
Bonnin *et al.*[10]	Not reported	NO	None	Died before delivery	23rd week of pregnancy	Severe RV failure
McMillan *et al.*[46]	iv/sc heparin during pregnancy	NO	Aspirin	Caesarean section	1 day post-partum	Acute RV failure; intraperitoneal bleeding
McMillan *et al.*[46]	LMWH during pregnancy	NO, prostacyclin (initiated after decompensation)	Verapamil, aspirin, inotropic support	Caesarean section	1 day post-partum	Pulmonary thrombo-embolism and RV failure
Bonnin *et al.*[10]	sc heparin before and after delivery	None	Not reported	Caesarean section	21 days post-partum	Pulmonary thrombo-embolism and RV failure

LMWH, low molecular weight heparin; Hb, haemoglobin; Mg, magnesium; NO, nitric oxide; PE, pulmonary embolism.

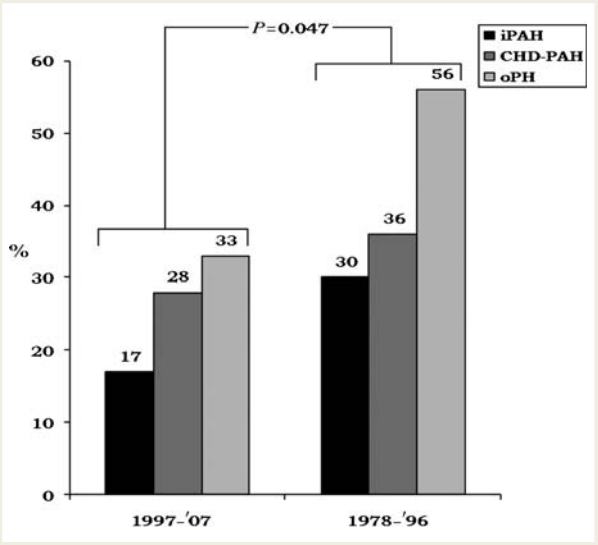

Figure 3 Maternal mortality amongst parturients with pulmonary arterial hypertension: Comparison between 1997–2007 and previous era (1978–1996).[1]

Discussion

Maternal death

Mortality rates among parturients with PAH remain prohibitively high, although they seem to have decreased in the last decade compared with previous era. Pregnancy should, therefore, continue to be discouraged in patients with PAH. Early contraception advice should be provided and termination should be considered if pregnancy occurs.[53–56]

Timing of maternal death

The majority of deaths among parturients with PAH in the last decade and in previous decades occurred in the peri-partum period, mainly within the first month from delivery.[1] This underscores the ongoing challenge of parturients with PAH to cope with the haemodynamic changes related to pregnancy, further exaggerated by acute changes during delivery and the post-partum. Pregnancy-induced systemic vasodilation and the increase in cardiac output may enhance right-to-left shunting and exacerbate pre-existing hypoxia in patients with CHD-PAH, leading to further pulmonary vasoconstriction. Further haemodynamic stress occurs during labour and delivery, when hypercarbia and acidosis may increase pulmonary hypertension acutely, leading to refractory right heart failure.[53,55–57] The latter was, in fact, the main cause of peri-partum death in our study.

The effects of pregnancy on the cardiovascular system persist for several months after delivery.[58] In this study, three late deaths were reported at 14, 19, and 24 months following delivery, but only nine (12%) patients were followed for more than 1 year. It is therefore purely speculative as to whether pregnancy itself may have an adverse effect on cardiopulmonary function,[59] leading to premature death, or simply we have seen the guarded prognosis and natural history of PAH, or both.

Idiopathic pulmonary hypertension versus congenital heart disease-associated pulmonary arterial hypertension and other pulmonary arterial hypertension

Maternal mortality in patients with iPAH was lower than in CHD-PAH and oPH patients, although this failed to reach statistical significance (possibly due to the low number of patients in individual groups). It is possible that the availability and more liberal use of advanced therapies in iPAH resulted in improved outcomes, even though our study was not powered to confirm this. The oPH group included patients with a variety of multisystem disorders such as systemic lupus erythematosus and diseases associated with a high risk of thrombo-embolic events such as the antiphospholipid syndrome.[60,61] CHD-PAH patients, mostly with Eisenmenger syndrome, are also predisposed to systemic complications such as bleeding and thrombotic diathesis, arrhythmias, and multiorgan involvement, which may contribute to the increased maternal mortality observed.[54,62] It is noteworthy that all maternal deaths in CHD-PAH occurred in the post-partum period and none antenatally, perhaps suggesting a relative advantage of the 'trained' right ventricle (subject to chronic pressure overload) in coping with the additional pregnancy load.

Correlates of maternal death

Primagravidae were found to be at higher risk of death in this study. This may simply reflect that parturients with previous successful pregnancies were likely at the better end of the spectrum of PAH, with perhaps a lower risk of complications during subsequent pregnancies.

Management of pregnant women with pulmonary arterial hypertension

Mode of delivery

The optimal mode of delivery (vaginal vs. caesarean section) in patients with PAH and/or CHD remains a matter of debate.[63] Vaginal delivery, however, is associated with smaller shifts in blood volume, fewer clotting or bleeding complications, and a lower risk of infection.[55,64] Caesarean section may become necessary in cases of maternal haemodynamic deterioration or foetal distress requiring urgent delivery. Compared with previous era,[1] fewer patients in this study had vaginal delivery, and the proportion of premature deliveries was higher. Closer surveillance and a lower threshold for intervention with early signs of maternal or foetal distress may have resulted in higher rates of caesarean section and premature delivery compared with previous era, but also, we speculate, in better outcomes.

Anaesthesia

A higher maternal mortality was found in patients who had general anaesthesia in the present study. This could reflect the higher risk of general anaesthetics in patients with PAH. General anaesthesia is known to depress cardiac contractility (volatile agents), increase pulmonary vascular resistance (positive pressure ventilation), and may result in an increase in pulmonary arterial pressure during laryngoscopy and intubation.[7] General or epidural anaesthesia should be performed by an experienced anaesthetist early during labour to avoid increase in cardiac output associated with contraction and pain.[55,57,65] We cannot, however, exclude the possibility that the relation between general anaesthesia and maternal mortality derives from the employment of caesarean section/general anaesthesia particularly in high-risk patients.

Peri-partum monitoring

Careful monitoring of arterial oxygen saturation, cardiac rhythm, and blood pressure are recommended for PAH patients in the peri-partum period.[66] An arterial line and a central venous catheter for the monitoring of right atrial pressure facilitate these measurements and should therefore be considered for parturients with PAH.[56,67] Invasive pulmonary arterial pressure monitoring remains controversial, however, owing to associated complications such as pulmonary artery rupture and the lack of evidence that it improves outcomes in these patients.[68] The use of direct pulmonary arterial pressure monitoring in more than half of the patients in our study should therefore be questioned. This high proportion did not translate in worse or better outcomes, although two (5%) patients developed tachyarrhythmia requiring catheter withdrawal.

Thromboprophylaxis

There is no standard thromboprophylaxis for pregnant women with PAH, especially for Eisenmenger patients with thrombotic and bleeding diathesis.[69] Low-dose subcutaneous heparin prophylaxis is generally recommended in pregnant women with PAH, but some patients may require higher levels of anticoagulation (e.g. patients with a history of thrombo-embolic events or atrial fibrillation).[53,56] Even though not reported as the primary cause of death, almost half of the CHD-PAH patients who died had peri-partum bleeding or a significant drop in haemoglobin concentration, which leads to haemodynamic instability and compromises oxygen carrying capacity[70] (*Table 2*).

Pulmonary thrombosis was responsible for the death of two (25%) patients with CHD-PAH (2 and 3 days after delivery); neither patient was receiving thromboprophylaxis. Pulmonary thrombosis was also responsible for two (50%) deaths in oPH, despite prophylactic anticoagulation. Both patients, however, were at high thrombotic risk owing to protein C deficiency and antiphospholipid syndrome, respectively. No deaths from pulmonary thrombosis were reported in iPAH, where 50% of patients received thromboprophylaxis. Although our study cannot specify the type and extent of thromboprophylaxis required for pregnancy and PAH, its timely consideration needs to be discussed within the multidisciplinary team and agreed with the patient.

Advanced pulmonary arterial hypertension therapies

Over the past decade, advanced therapies (prostacyclin analogues, phosphodiesterase inhibitors, and endothelin-receptor antagonists) have revolutionized PAH management. Even though survival benefits from these therapies have not been yet demonstrated, improvements in exercise capacity and functional class have been consistently reported in iPAH.[4] Similar effects have been reported in patients with Eisenmenger syndrome on prostacyclin analogues and oral endothelin-receptor antagonist bosentan.[71–73] The effects of these advanced therapies on parturients with PAH remain, however, unknown.

Inhaled NO has also been shown to cause an acute drop in pulmonary vascular resistance in Eisenmenger syndrome,[74] iPAH,[75] and chronic pulmonary thrombo-embolic disease.[76] In this study, 19 pregnant women with PAH received NO, 6 (32%) of whom died. Nitric oxide was, however, often administered as a last resort when patients were already haemodynamically unstable, begging the question of the potential effect of NO or other advanced therapy when administered electively earlier during pregnancy and labour.[10,38,46]

Prostacyclin analogues were administered in 30 (41%) patients, 6 (20%) of whom died. As with NO, prostacyclin was commenced late, when patients were already unstable or had developed symptoms of refractory heart failure. Advanced therapy should, possibly, be instituted early, prior to cardiopulmonary decompensation. Animal studies have shown that bosentan may have teratogenic effects[77] and is, thus, contraindicated during pregnancy; the small number of parturients on bosentan found in this review is therefore not surprising. One Eisenmenger patient in our study was on bosentan before conception and was kept on a combination of bosentan and sildenafil throughout pregnancy, resulting in the birth of a healthy infant. A further patient with iPAH received bosentan therapy post-partum.

Animal studies on sildenafil and two case reports on humans have reported no deleterious effects on the mother or offspring.[78] However, sildenafil received approval by the Food and Drug Administration for the treatment of PAH only in 2005. Therefore, only five (7%) parturients in this study received sildenafil, four with CHD-PAH, and one with iPAH; none of them died.

Calcium channel blockers are safe during pregnancy[79] and may prevent pre-term labour,[80] a common complication in patients with PAH, seen in 85% of parturients in this study. However, calcium channel blockers may be beneficial only in responders to vasoreactivity tests, and only 6.8% are reported to have a long-term benefit.[3,81]

Clinical implications

Women with PAH should be counselled in early adolescence about pregnancy risks and appropriate contraception. When a patient with known or newly diagnosed PAH, however, becomes pregnant, close follow-up in a tertiary centre with a multidisciplinary team including cardiologists, obstetricians, anaesthetists, and neonatologists with experience in high-risk pregnancies appears mandatory.[53,56,66] Frequent visits throughout pregnancy are recommended, and hospitalization during the third trimester may facilitate management and safer delivery. Detailed plans including timing and mode of delivery should be discussed in advance, agreed with the patient, and communicated with the local health professionals.[55,66] Advanced PAH therapies and effective thromboprophylaxis must be considered before patients decompensate or thrombotic complications ensue. Maternal safety and well-being need to be weighed against premature delivery, intrauterine growth restriction, and the need for neonatal care, when decisions about timing and type of delivery for the individual patient are made.

Study limitations

Our systematic review included all 73 cases published during the last decade and utilized pooled data to estimate overall mortality. We cannot, thus, exclude publication bias towards cases with a favourable outcome, resulting in an artificially lower mortality. Moreover, very few patients were followed for more than 1 year; therefore, the number of late deaths could have been underestimated. However, comparison was made with previous studies of a similar nature and if a publication bias is present, it does not subtract from our key message; although there has been some improvement in pregnancy outcomes in PAH patients in recent years, pregnancy-related mortality remains high. Larger, possibly, multicentre, prospective studies are required to determine the exact pregnancy-related risk in PAH, identify additional predictors of outcome, and firmly establish the role of advanced PAH therapies in this setting.

Conclusion

Maternal mortality in parturients with PAH remains prohibitively high despite lower death rates over the last decade compared with previous era. Early advice on the risks of pregnancy and methods of contraception is, thus, paramount. Women with PAH who become pregnant should be followed by a multidisciplinary team, and advanced PAH therapies should be given consideration in a timely fashion.

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Conflict of interest: none declared.

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