Pulmonary hypertension and pregnancy outcomes: data from the Registry Of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology

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Aims To describe the outcomes of pregnancy in women with pulmonary hypertension.

Methods and results In 2007 the European Registry on Pregnancy and Heart Disease was initiated by the European Society of Cardiology. Consecutive patients with all forms of cardiovascular disease, presenting with pregnancy, were enrolled with the aim of investigating the pregnancy outcomes. This subgroup of the cohort included 151 women with pulmonary hypertension (PH) either diagnosed by right heart catheterization or diagnosed as possible PH by echocardiographic signs, with 26% having pulmonary arterial hypertension (PAH), in three subgroups: idiopathic (iPAH), associated with congenital heart disease (CHD-PAH), or associated with other disease (oPAH), and 74% having PH caused by left heart disease (LHD-PH, $n = 112$). Maternal mean age was 29.2 ± 5.6 years and 37% were nulliparous. Right ventricular systolic pressure was <50 mmHg in 59.6% of patients, 50–70 mmHg in 28.5% and >70 mmHg in 11.9%. In more than 75% of patients, the diagnosis of PH had been made before pregnancy. Maternal death up to 1 week after delivery occurred in five patients (3.3%), with another two out of 78 patients who presented for follow-up (2.6%), dying within 6 months after delivery. The highest mortality was found in iPAH (3/7, 43%). During pregnancy, heart failure occurred in 27%. Caesarean section was performed in 63.4% (23.9% as emergency). Therapeutic abortion was performed in 4.0%. Complications included miscarriage (5.6%), fetal mortality (2%), premature delivery (21.7%), low birth weight (19.0%), and neonatal mortality (0.7%).

Conclusion Mortality in this group of patients with various forms of PH was lower than previously reported as specialized care during pregnancy and delivery was available. However, maternal and fetal mortality remains prohibitively high in women with iPAH, although this conclusion is restricted by limited numbers. Early advice on contraception, pregnancy risk and fetal outcome remains paramount.

Keywords Left heart disease • Rheumatic heart disease • Management • Congenital heart disease

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Introduction

Pulmonary hypertension (PH) is a pathophysiological condition, often leading to debilitating symptoms and shortened overall life expectancy, caused by narrowing of the pulmonary vasculature and often leading to right heart failure. Pregnancy in women with PH, including idiopathic pulmonary arterial hypertension (iPAH), PH associated with congenital heart disease (CHD-PAH) or PAH caused by other conditions (oPAH), is known to be associated with a high maternal mortality (between 25% and 56%).[1,2] Pulmonary hypertension in pregnant women is a modified World Health Organization (WHO) Class IV indication and, therefore, pregnancy should be avoided.[3] Pregnancy outcome is poor with high rates of preterm delivery (85–100%), fetal growth restriction (3–33%), and fetal/neonatal loss (7–13%).[1,2,4] However, despite the advice to avoid pregnancy,[3,5] some women with PH choose to become pregnant or to continue with an unplanned pregnancy.

Owing to the absence of larger (>20 cases) prospective outcome studies on PH in pregnancy, many questions remain unanswered. The aim of the present report was to investigate maternal and fetal outcomes in women with PH, including all subtypes of PH, according to the most recent guidelines[6] and to document the outcomes in the different subpopulations. The specific impact of comorbidities, type of anaesthesia, mode of delivery, and medication were evaluated, as well as the risk of developing heart failure and thrombotic events in the mother. The data were collected by the European Registry Of Pregnancy and Cardiac Disease (ROPAC). This registry was initiated by the European Society of Cardiology (ESC) in 2007. Consecutive patients with all forms of cardiovascular disease presenting with pregnancy were enrolled.[7] By 2014, 151 women with elevated pulmonary artery pressures, diagnosed either by right heart catheterization or as possible PH by echocardiographic signs, were included.

Methods

Study design

A detailed description of study design and data collection was reported previously.[7] ROPAC is an ongoing worldwide registry that includes all pregnant women with congenital and structural heart disease. Patients with arrhythmic disease in the absence of structural heart disease are excluded. Prospective inclusion of patients commenced in January 2008, and this interim analysis concerns patients enrolled between January 2008 and April 2014.

For the present study, outcomes of pregnancy were analysed for patients with PH. All patients with right ventricular systolic pressure (RVSP) >30 mmHg at rest, measured by echocardiography or right heart catheterization, were included. Patients with elevated RVSP caused by outflow tract obstruction/pulmonary stenosis were excluded.

Data

Information was collected regarding age, parity, cardiovascular risk factors, type of heart disease, aetiology of PH, previous interventions, New York Heart Association (NYHA) functional class,[8] signs of heart failure, rhythm disturbance, medication, maternal or fetal mortality, cardiac events such as heart failure or arrhythmias, obstetric events such as pre-eclamptic toxaemia or postpartum haemorrhage, timing and mode of delivery, neonatal sex and birth weight, and postpartum events. Follow-up data included vital status, cardiac events and neonatal status. Follow-up was available in all patients up to 1 week. If available, follow-up was reported up to 6 months.

Information on pulmonary hypertension was collected via the following ROPAC Registry website CRF variables: under echocardiographic assessment the value of peak velocity tricuspid regurgitation, as well as RVSP could be entered; RVSP could be entered via a tick box in the following categories of <30, 30–50, 50–70, 70–90, and >90 mmHg or unavailable; among the parameters for the cardiac function the right ventricular function could be entered as normal, moderately impaired and severely impaired.

The question of whether full right heart catheterization confirming PH via standard criteria was performed before pregnancy, could be answered with either a yes (26%) or no. No other parameters such, for example, cardiac output, or pulmonary vascular resistance, were collected in this database.

Pregnant women were categorized based on their PH aetiology, as classified in the most recent consensus document.[9] Patients with PAH in case of iPAH, CHD-PAH or oPAH caused by diseases such as connective tissue disease or vascular malformations were classified as group 1. Patients with PH caused by left heart disease (LHD-PH) with left ventricular systolic dysfunction, valvular disease or congenital/acquired left heart inflow or outflow tract obstructions or congenital cardiomyopathies were classified as group 2. Other diagnoses mentioned in the consensus documents were not present in our study population.

Patients were stratified by RVSP level in three groups: 30–50 mmHg, 50–70 mmHg, and >70 mmHg.

Heart failure was defined according to ESC guidelines,[8] as a clinical syndrome that is characterized by specific symptoms (dyspnoea and fatigue) and signs (fluid retention, such as oedema, rales) on physical examination, as judged by the treating cardiologist. An episode of heart failure during or after pregnancy was only registered when signs or symptoms of heart failure were present which required new treatment, change of treatment, or hospital admission.

Statistical analysis

Baseline characteristics, as well as cardiac, obstetric and fetal outcome are presented for the total PH group. We compared baseline characteristics and outcome of PH in group 1 and group 2. Categorical data are presented as frequencies and percentages, and chi-square tests were used for comparison. If there were less than five cases in a group, Fisher's exact test was used. Normality of continuous data was checked with Kolmogorov–Smirnov tests and presented either as mean ± standard deviation, or as median and first and third quartiles (Q1–Q3) as appropriate. Differences between groups were assessed using Student's *t*-tests or, in case of non-normality, using Mann–Whitney tests. *P*-values were considered statistically significant if less than 0.05 (two-sided test). All analyses were performed with SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

In total, 2966 pregnancies were enrolled in this interim analysis and 151 (5.1%) had PH (see the Supplementary material online *Figure S1*). Of these women, 39 (26%) had PAH (*Table 1*). This

Table 1 Classification of pregnant women with pulmonary hypertension

Aetiology of pulmonary hypertension	*n*	%
Group 1 (*n* = 39, 25.9%)		
Idiopathic PAH	7	4.6%
PAH in congenital heart disease		
Eisenmenger syndrome	6	4.0%
PAH in left-to-right shunts	7	4.6%
Post-operative PAH	15	9.9%
Other PAH	4	2.6%
Group 2 (*n* = 112, 74.1%)		
Left heart disease		
Valvular		
Aortic stenosis	11	7.3%
Aortic regurgitation	7	4.6%
Mitral stenosis	54	35.8%
Mitral regurgitation	26	17.2%
Other valve disease	2	13.2%
Cardiomyopathy		
Dilated CMP	1	0.7%
Hypertrophic CMP	2	1.3%
PPCM	4	2.6%
Myocarditis	2	1.3%
Other CMP	2	1.3%
ccTGA, with systemic ventricular dysfunction	1	0.7%

ccTGA, congenitally corrected transposition of the great arteries; CMP, cardiomyopathy; PAH, pulmonary arterial hypertension; PPCM, peripartum cardiomyopathy.

was either idiopathic, associated with congenital heart disease, or associated with other disease (e.g. connective tissue disease or vascular malformations). It was found that LHD-PH was present in 112 (74%) patients and was associated with valvular heart disease in 100 women and with cardiomyopathy in 12 women (*Table 1*). The mean age of the 151 PH patients was 29.2 ± 5.6 years and 56 of them (37%) were nulliparous. The majority (59.6%) had a mildly elevated RVSP between 30 and 50 mmHg. Further baseline characteristics are presented in *Table 2*.

In more than 75% of the patients the diagnosis of PH had been made before pregnancy. There were no differences between women diagnosed before and during pregnancy.

Management

Management of PH patients is presented in *Table 2*. In six women (4.0%), therapeutic abortion was performed because of the PH in the mother. This occurred in two (28.6%) of the iPAH patients, three (10.7%) of the CHD-PH patients, none (0.0%) of the oPAH patients, and in one (0.9%) of the LHD-PH patients ($P = 0.003$).

A total of 41 patients (27.2%) were administered diuretics during pregnancy (34 were LHD-PH patients). Fourteen patients (9.3%) took digoxin during pregnancy (13 were LHD-PH patients). Four of these used digoxin temporarily (only one trimester).

During pregnancy, nine patients received advanced PH medication (see the Supplementary material online, *Table S1*)—all of them were given a phosphodiesterase type 5 inhibitor (PDE5-i). In addition, four of these nine patients were administered an endothelin-receptor antagonist (ERA), and three patients were given a prostacyclin analogue. One of these patients used all three. Of the patients on ERA, one patient developed a postpartum pulmonary embolism as well as heart failure, and one patient was reported to have a thromboembolic complication leading to temporary blindness for 5 days. Heart failure occurred in three other patients, all of whom were taking PDE5-i.

Maternal outcomes

Hospitalization was needed in 75 patients with 26 of them being admitted more than once. In 52 patients there was a cardiac reason for admission. Median timing of admission (known in 73% of cases) was 27 weeks (Q1–Q3 = 19.6–35.1). Admission for cardiac issues occurred at a median of 25.1 weeks (Q1–Q3 = 19.2–31.2) and mainly for heart failure (42 patients).

No deaths occurred during pregnancy. Five women (3.3%) died peripartum up to 1 week after delivery. Another two (2.6%) of 78 women in whom follow-up was available died within 6 months after delivery. Details of maternal mortality are presented in *Table 3*. Death most commonly occurred in the iPAH group (3/7, 43%), followed by patients with LHD-PH (3/112, 2.7%). One of the patients with CHD-PAH died (1/28, 3.6%). The five patients who died in the first week postpartum died shortly after a preterm spontaneous or induced delivery and the cause of death was acute cardiac failure. In two patients this was induced by an infection (patient numbers 4 and 6) and in one patient by mechanical valve thrombosis (patient number 5). Two patients died during an intervention (abortion in patient number 2 and hysterotomy in patient number 3). One of these seven patients reached term pregnancy and died of cardiogenic shock 24 weeks after delivery (patient number 1). One patient had sudden death because of maternal heart failure 24 weeks after therapeutic abortion was performed (patient number 7).

Some women suffered from thrombotic events. One patient, with a closed arterial duct, had a pulmonary embolism and four patients suffered from other thrombotic complications (prosthetic valve thrombosis, $n = 1$; ischaemic cerebrovascular event, $n = 3$). The ischaemic cerebrovascular events occurred in the presence of a mechanical aortic valve ($n = 1$), mitral valve stenosis ($n = 1$), and an unrepaired arterial duct.

Figure 1 shows the outcome of pregnancy in three different groups: mildly, moderately, and severely elevated RVSP. Maternal mortality at 6 months' follow-up was significantly different in the three groups (0% in mild PH, 0% in moderate PH, and 25% in severe PH). There were non-significant differences in the rate of low birth weight (<2500 g) in the children of women with severe PH ($P = 0.09$, *Figure 1*). However, in analysis of the data by type of PH (*Figure 2*), more women with CHD-PAH and oPAH had babies with a birth weight <2500 g.

Delivery

Details of delivery were reported in 145 patients (96.0%). Caesarean section (CS) was performed in 92 patients (63.4%) and was

Table 2 Baseline characteristics, management and outcome of pregnant women

	PH, $n=151$		Group 1						Group 2		*P*-value of difference between four diagnostic groups
			iPAH, $n=7$		CHD-PAH, $n=28$		oPAH, $n=4$		LHD-PH, $n=112$		
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	
Baseline characteristics											
Age, years (SD)	29.2	(±5.6)	29.9	(±7.2)	28.7	(±5.8)	32.3	(±5.0)	29.2	(±5.6)	0.69
Nulliparous	56	(37.1)	3	(42.9)	14	(50.0)	3	(75.0)	36	(32.1)	0.11
Diagnosis made*											0.36
Before pregnancy	88	(71.5)	4	(66.7)	21	(87.5)	2	(50.0)	61	(68.5)	
During pregnancy	35	(28.5)	2	(33.3)	3	(12.5)	2	(50.0)	28	(31.5)	
NYHA class											0.86
I	76	(51.0)	4	(57.1)	12	(42.9)	1	(25.0)	59	(53.6)	
II	47	(31.5)	2	(28.6)	10	(35.7)	2	(50.0)	33	(30.0)	
III	22	(14.8)	1	(14.3)	6	(21.4)	1	(25.0)	14	(12.7)	
IV	4	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)	4	(3.6)	
Signs of heart failure	31	(20.5)	1	(14.3)	8	(29.6)	1	(25.0)	21	(18.9)	0.58
Right ventricular systolic pressure											0.053
30–50 mmHg	90	(59.6)	3	(42.9)	12	(42.9)	3	(75.0)	72	(64.3)	
50–70 mmHg	43	(28.5)	2	(28.6)	9	(32.1)	1	(25.0)	31	(27.7)	
70–90 mmHg	8	(5.3)	0	(0.0)	2	(7.1)	0	(0.0)	6	(5.4)	
>90 mmHg	10	(6.6)	2	(28.6)	5	(17.9)	0	(0.0)	3	(2.7)	
Management											
Delivery, median weeks of pregnancy (Q1–Q3)	38.0	(37.0–39.0)	37.4	(32.1–38.6)	38.1	(36.1–39.3)	36.6	(34.6–38.8)	38.0	(37.0–39.0)	0.47
Mode of delivery**											
Vaginal	53	(35.8)	1	(20.0)	6	(24.0)	0	(0.0)	45	(40.9)	0.004
Caesarean section	92	(63.4)	4	(80.0)	19	(74.0)	4	(100)	65	(59.1)	0.23
Emergency caesarean section	22	(23.9)	0	(0.0)	2	(10.5)	1	(25.0)	19	(29.2)	0.29
General anaesthesia during caesarean section	21	(32.3)***	0	(0.0)	5	(33.3)	1	(33.3)	15	(34.1)	0.78
Antithrombotic therapy											
During pregnancy: therapeutic	34	(22.5)	4	(57.1)	2	(7.1)	0	(0.0)	28	(25.0)	0.016
During pregnancy: antiplatelet only	3	(2.0)	0	(0.0)	3	(10.7)	0	(0.0)	0	(0.0)	0.027
During pregnancy: other	18	(11.9)	2	(28.6)	9	(32.1)	0	(0.0)	7	(6.2)	0.001
Calcium channel blockers	6	(4.0)	3	(42.9)	0	(0.0)	0	(0.0)	3	(2.7)	0.003
Outcome											
Maternal death											
During pregnancy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	na
Postpartum (<1 week)	5	(3.3)	2	(28.6)	0	(0.0)	0	(0.0)	3	(2.7)	0.35
Postpartum (>1 week; <6 months)	2	(2.6)****	1	(16.7)	1	(6.7)	0	(0.0)	0	(0.0)	0.057
Other complications											
Pulmonary thromboembolism	1	(0.6)	0	(0.0)	1	(3.6)	0	(0.0)	0	(0.0)	0.26
Other thromboembolic events	4	(2.6)	0	(0.0)	1	(3.6)	0	(0.0)	3	(2.7)	0.69
Heart failure	42	(27.8)	2	(28.6)	10	(35.7)	2	(50.0)	28	(25.0)	0.42
Postpartum haemorrhage	6	(4.0)	0	(0.0)	0	(0.0)	0	(0.0)	6	(5.4)	0.75
Supraventricular tachyarrhythmias	5	(3.3)	0	(0.0)	1	(3.6)	0	(0.0)	4	(3.6)	1.00
Ventricular tachyarrhythmias	6	(4.0)	0	(0.0)	3	(10.7)	0	(0.0)	3	(2.7)	0.28
Pre-eclamptic toxaemia	2	(1.3)	1	(14.3)	0	(0.0)	0	(0.0)	1	(0.9)	0.17

*not reported in 28 cases, **not reported or not applicable in 6 cases, ***not reported in 27 cases, ****follow-up available in 78 cases.
CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; iPAH, idiopathic pulmonary arterial hypertension; LHD-PH, pulmonary hypertension caused by left heart disease; NYHA, New York Heart Association; oPAH, pulmonary arterial hypertension associated with other disease; PH, pulmonary hypertension.

initially planned in 83 (90.2%), mainly for cardiac reasons (65.1%). A spontaneous start of labour was reported in 10 patients. Anaesthesia was reported in 65 CS patients: in 21 patients (32.3%), CS was performed under general anaesthesia and in 44 patients (67.7%) under local anaesthesia. Emergency CS was reported in 21 patients, and in eight this was for cardiac reasons (heart failure or anticoagulation). Heart failure occurred in five patients (11.4%) after general anaesthesia and in three patients (14.3%) after local anaesthesia in the peripartum period and up to 1 week postpartum. Maternal death occurred in two patients (9.1%) after emergency CS; two patients (2.9%) died after planned non-emergency CS within 1 week after delivery and one patient died during therapeutic abortion ($P=0.25$, *Table 3*).

Vaginal delivery was performed in 53 patients (36.6%). Twenty-three patients (43.4%) had an induced vaginal labour. Heart failure peripartum or in the first week postpartum occurred in two patients (3.8%) after vaginal delivery and in 12 patients (13.0%) after CS ($P=0.07$). No maternal mortality within 1 week postpartum occurred in patients after vaginal delivery compared with 4.3% in the CS group ($P=0.19$).

Fetal outcome

Fetal or neonatal death up to 1 week after delivery occurred in 14 pregnancies (9.3%). There were 20 neonates (13.8%) who were small for gestational age (*Table 4*). Of these, 13 babies had a birth

Table 3 Cases of maternal death

Patient	Region	Age	Diagnosis	Diagnosis known before pregnancy	Medical history	RVSP (mmHg)	Parity	Pre-pregnancy counselling	NYHA before pregnancy	Events during pregnancy	Pregnancy duration (weeks)	Delivery	Fetal status	Timing of maternal death	Cause of death	Additional details
1	Mediterranean	29	Idiopathic PAH	No		>90 (after delivery)	G1P0	No	I	Puerperal PET	39	Induced vaginal delivery, epidural anaesthesia	Alive	24 weeks postpartum	Oligoanuric cardiogenic shock	Treated with diuretics and vasoactive drugs
2	Mediterranean	23	Idiopathic PAH	Yes		50–70	G2P0A1	Yes	II		7	Therapeutic abortion because of maternal condition	Abortion	During therapeutic abortion	Syncope during therapeutic abortion	Trial medication: tadalafil and ambrisentan vs. placebo
3	North Africa	17	Idiopathic PAH	Yes	Heart failure and PET in previous pregnancy	>90	G2P0A1	No	III	PET followed by heart failure at 28 weeks; IUFD	29	Hysterotomy for IUFD under general anaesthesia	Death	During 'delivery'	RV failure, shock during hysterotomy	Treated with diuretics and calcium channel blocker
4	Mediterranean	35	Aortic and mitral mechanical valve; rheumatic disease; LV dysfunction	Yes	Heart failure in previous pregnancy	50–70	G3P2	Yes	II	Heart failure and pneumonia	24	Induced labour, emergency CS for maternal shock under general anaesthesia	Alive	5 days postpartum	Cardiac shock caused by H1N1 pneumonia	Beta-blocker and diuretics, VKA throughout pregnancy
5	North Africa	17	Mitral mechanical valve; rheumatic disease	Yes	History of stroke	30–50	G1P0	Yes	I	Increased valve gradient	34	Spontaneous labour, planned CS because of valve gradient	Alive	2 days postpartum	Mechanical valve thrombosis	VKA throughout pregnancy,* then treated with streptokinase, no surgery available
6	North Africa	18	Aortic and mitral regurgitation; rheumatic disease	Yes		50–70	G2P1	Yes	II		33	Spontaneous labour (PROM), emergency CS because of fetal distress	Death	2 days postpartum	Septic shock	Postpartum heart failure, PPH and persistent chest infection with poor response to therapy
7	Africa	20	Eisenmenger, muscular VSD	Yes	Cyanosis <85%	70–90	G1P0	No	III	Ventricular arrhythmia, heart failure in 12th week	14	Therapeutic abortion because of maternal condition	Abortion	24 weeks postpartum	Sudden death	

*First trimester anticoagulation unknown.

CS, caesarean section; G, gravida; IUFD, intrauterine fetal death; LV, left ventricular; NYHA, New York Heart Association; oPAH, pulmonary arterial hypertension associated with other disease; P, para; PET, pre-eclamptic toxaemia; PPH, postpartum haemorrhage; PROM, premature rupture of membranes; RV, right ventricular; RVSP, right ventricular systolic pressure; VKA, vitamin K antagonist; VSD, ventricular septal defect.

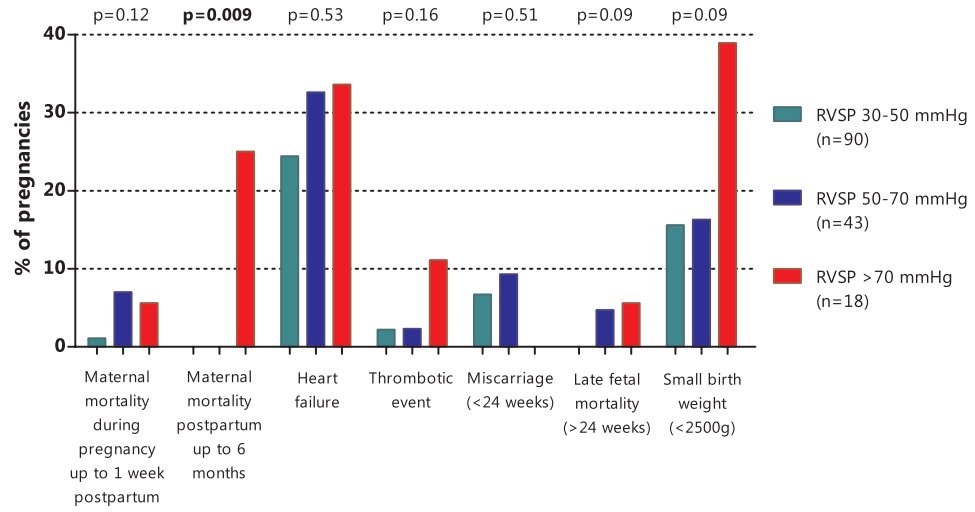

Figure 1 Outcome of pregnancy and level of right ventricular systolic pressure (RVSP).

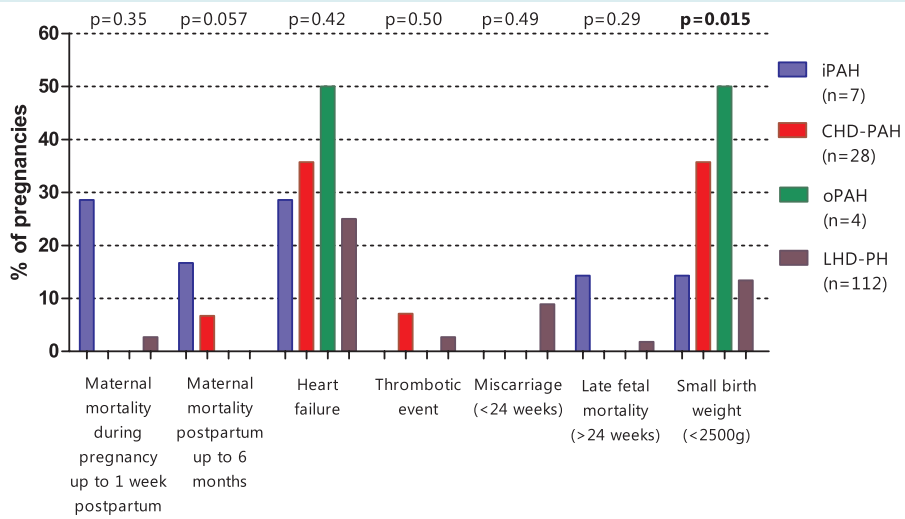

Figure 2 Outcome of pregnancy per pulmonary hypertension (PH) group. iPAH, idiopathic pulmonary arterial hypertension; CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; oPAH, pulmonary arterial hypertension associated with other disease; LHD-PH, pulmonary hypertension caused by left heart disease.

weight <2500 g. A birth weight <2500 g occurred in 28 neonates (19.3%). Twenty-five of these were delivered by CS, which accounts for 27.2% of CS deliveries vs. three (5.7%) vaginal deliveries ($P = 0.002$). Eight of these 25 were emergency CS deliveries.

Six neonates (4.0%) were reported to have cardiac anomalies: one persistent ductus arteriosus; one a combination of persistent ductus arteriosus and atrial septal defect; one a combination of persistent ductus arteriosus, atrial septal defect, and pulmonary stenosis; one hypertrophic cardiomyopathy; one pulmonary valve stenosis; one a combination of total anomalous pulmonary venous return and atrial septal defect. Of these six neonates, four had a mother with LHD-PH (4 out of 99 live births in LHD-PH; 4%) and two had a mother with CHD-PAH (2 out of 25 live births in CHD-PAH; 8%). Atrial septal defect was found in a mother with CHD-PAH that used a PDE5-i.

Six other neonates were reported to have the following non-cardiac anomalies: congenital haemophagocytic syndrome, hydrocoele, respiratory distress syndrome, rhesus isoimmunization, and wet lung.

Follow-up at 6 months postpartum

In 78 patients (51.7%) follow-up at 6 months postpartum was available. Baseline characteristics of patients with and without follow-up are presented in the Supplementary material online, *Table S2*. Two of these patients (2.6%, *Table 2* and *Table 3*) died 24 weeks after

Table 4 Fetal and neonatal outcome

Fetal complications	PH, $n = 151$		Group 1						Group 2		*P*-value of difference between four diagnostic groups
			iPAH, $n = 7$		CHD-PAH, $n = 28$		oPAH, $n = 4$		LHD-PH, $n = 112$		
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	
Premature delivery (<37 weeks)	26	(21.7)	1	(25.0)	7	(29.2)	2	(50.0)	16	(18.2)	0.20
Low birth weight (<2500 g)	28	(19.0)	1	(14.3)	10	(35.7)	2	(50.0)	15	(13.4)	0.015
Miscarriage <24 weeks	10	(6.6)	0	(0.0)	0	(0.0)	0	(0.0)	10	(8.9)	0.49
Fetal mortality >24 weeks	3	(2.0)	1	(14.3)	0	(0.0)	0	(0.0)	2	(1.8)	0.29
Neonatal mortality <1 week	1	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	1.00

CHD-PAH, pulmonary arterial hypertension associated with congenital heart disease; iPAH, idiopathic pulmonary arterial hypertension; LHD-PH, pulmonary hypertension caused by left heart disease; oPAH, pulmonary arterial hypertension associated with other disease; PH, pulmonary hypertension.

delivery. Heart failure occurred in one of the patients who died, as well as in five other patients (7.8%), and two patients (2.6%) had an arrhythmic event.

In 22 patients (14.6%) echocardiography before and after pregnancy was available and no significant change in RVSP category was found.

Discussion

In this prospective, contemporary, international registry of 151 pregnant women with PH, the incidence of maternal cardiac and neonatal complications was high. However, with a maternal mortality for the entire group of less than 5%, the overall outcome was substantially better than previously reported. It is the first larger cohort including pregnant women with PH categorized according to the most recent consensus document. A clear distinction in maternal morbidity and mortality could be made between the different forms. Pulmonary hypertension resulting from left heart disease was the most common form of PH in this cohort and, to a large extent, was caused by mitral valve disease or complicated peripartum cardiomyopathy.

Pulmonary hypertension caused by left heart disease, classified as group 2 of the most recently updated classification on PH,[9] is believed to be the most common cause of PH globally. Epidemiological studies of group 2 PH are less exhaustive than for the rarer causes of PH such as iPAH.[10] Group 2 PH is likely to be caused by passive downstream elevation in the left heart pressures (postcapillary), but may progress to reactive changes of the pulmonary arteries (precapillary), leading to mixed PH.[11] For reasons unknown, only a certain proportion of patients progress to develop reactive pulmonary vasoconstriction, despite the presence of chronic heart failure. Our data show that the diagnosis of PH was made in the majority of cases before pregnancy, with more than 80% of women having no or minimal symptoms (NYHA functional class I or II). We found a lower mortality in women with LHD-PH (3 of 112 cases) and CHD-PAH (1 of 28 cases) compared with a mortality of 43% (3 of 7 cases) in women with iPAH, with most of the deaths occurring postpartum. The latter deserves special attention as it implies that all women with PH should remain under close supervision for at least a week after having given birth. Heart failure occurred in almost 30% and arrhythmias were common. Forty-one patients received diuretics during pregnancy, but advanced PH therapy was only given to nine cases (8 of 39 cases in group 1, predominantly with iPAH, and 1 of 112 cases in group 2).

Tabarsi *et al.*[12] recently reported their experience with epoprostenol (the first approved therapy shown to improve morbidity and mortality in PAH) in a woman with severe PAH and right ventricular dysfunction. The outcome for this woman was satisfactory up to 2 years post-delivery. However, the authors stress the importance of early contact with a highly experienced obstetrician in the course of a pregnancy and management by a multidisciplinary team. This team will also prepare a delivery plan, balancing the advantages of vaginal birth (lower blood loss, lower risk of infection, and thrombus formation) vs. CS (better haemodynamic monitoring). The 2015 ESC/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension,[6] as well as the ESC guidelines on cardiovascular disease in pregnancy,[3] state that pregnancy in all women with PH should be avoided or terminated early. Our data suggest that such advice should be focused on the high-risk subgroups, namely those with PAH. However, should pregnancy occur, very close expert follow-up is needed with at least monthly review. Serial echocardiography should be used to screen for right heart failure.

Overall, little is known about the outcome of PH in the peripartum period. There are only two systematic overviews and selected case series (<20 patients). The case series have mainly focused on PAH, such as the study by Jais *et al.*[13] reporting on the outcome of 26 pregnancies in 13 participating centres, during a 3-year period. Three women (12%) died and one woman needed urgent heart–lung transplantation. Women with well-controlled PAH and a low pulmonary vascular resistance in modern therapy had a better outcome in this cohort. A study by Weiss *et al.*,[2] reported on the pooled analysis of publications from 1978 to 1996 on a total of 125 cases, including 73 with Eisenmenger syndrome, 27 with primary PH, and 25 with secondary PH, with a mortality of 36%, 30%, and 56%, respectively. Of the total number of reported deaths ($n = 48$), 20% occurred late (as late as several months after delivery). Haemoglobin was reported for only 43 patients and

pulmonary artery pressure (PAP) for only 81 patients of the 125 patients. A more recent study by Bedard *et al.*[1] summarized the findings from 73 pregnant patients with PAH, with 29 having iPAH, 29 CHD-PAH, and 15 oPAH, with a 90-day reported mortality of 17%, 28%, and 33%, respectively. More than two-thirds of the deaths occurred within the first month after delivery. Patients with LHD-PH were not included in this analysis. As most of the cases in this cohort came from individual case reports, mean pulmonary artery pressure (MPAP), when not reported, was approximated or echocardiographic data was utilized using the Bernoulli formula (MPAP = systolic PAP estimated by echocardiogram/4 × 2.4). In the study by Bedard *et al.*,[1] therapies for PAH were used during pregnancy and delivery in 72% of patients with iPAH, 52% of patients with CHD-PAH, and 47% of patients with oPAH. Patients receiving general anaesthesia were four times more likely to die compared with patients receiving regional anaesthesia.

Recommendations for the management of pregnant women with PAH have been published recently in a state-of-the-art review.[14] However, this may not be applicable to pregnancy in women with other forms of pulmonary vascular disease as the use of PDE5-i and prostacyclin have not been investigated in those types of pregnancies.[6]

Role of echocardiography in our cohort in estimating the degree of pulmonary hypertension

According to the 2015 ESC/ERS guidelines for the diagnosis of PH,[6] right heart catheterization is recommended as a Class IC indication in patients with PAH. Right heart catheterization for patients with PH caused by left heart disease has an IIB indication and is indicated only to support treatment decisions. Right heart catheterization would therefore not have been indicated in pregnant women in PH groups II–V. The challenges in diagnosing the most frequent causes of PH have recently been summarized in a paper by Hoeper *et al.*[15]

The recently published guidelines also highlight the use of echocardiographic probability of PH in symptomatic patients with a suspicion of PH. The authors of the guidelines preferred the use of peak tricuspid regurgitation velocity over the estimated pulmonary artery systolic pressure or RVSP. However, in the ROPAC database peak tricuspid regurgitation velocity was only rarely entered by the investigators as it was not a mandatory field.

The majority of women in the ROPAC registry had mildly to moderately elevated RVSP with more than 80% having a RVSP <70 mmHg. Transthoracic echocardiography allows estimation of the RVSP from the velocity of the tricuspid regurgitation by adding right atrial pressure.[11] This diagnostic module has led to widespread use and increased documentation of the burden of PH in patients with heart disease and its association with a high morbidity and mortality. However, PH is often a neglected issue and the importance of long-term follow-up has only recently been highlighted.[16]

A rationale for using echocardiography in the diagnosis of PH in patients from low-to-middle income countries, where right heart catheterization is often not available, has been summarized recently.[17] According to our knowledge, the impact of the haemodynamic changes of pregnancy on the measurement of the RVSP by echocardiography has not been formally evaluated. However, in more than 75% of patients the diagnosis of PH had been made before pregnancy using standard criteria.

Recommendations for the management of pregnant women with PAH have been published in the ESC/ERS guidelines for the treatment and management of PH.[6] Patients with PAH who choose to continue pregnancy should be treated with disease-targeted therapy. However, this may not be applicable to pregnancy in women with other forms of PH as the use of PDE5-i and prostacyclin has not been investigated in these types of pregnancies. This may have been the reason why only nine patients in our cohort have received PH medication during pregnancy.

Fetal complications and outcomes

Perinatal complications were common, with fetal or neonatal demise occurring in almost 10%. Further, a birth weight of less than 2500 g occurred in one-fifth of the babies, reflecting the high rates of growth restriction and preterm birth. The long-term impact of chronic maternal hypoxia on fetal outcome remains unknown, but fetal growth restriction is known to programme increased rates of diabetes, heart disease, and hypertension in later life.[18] Poor fetal growth has been noted in most reports relating heart disease with pregnancy outcome, with the combination of hypoxia and impaired cardiac output having the most deleterious effect.

Data on the pulmonary circulation during pregnancy and its influence on the placental flow is scarce. However, it is known that MPAP in a normal pregnancy does not change,[19] while pulmonary flow increases. This implies that pulmonary vascular resistance has to decrease. In women with PH, it is likely that there is a limited ability of pulmonary vascular resistance to change throughout pregnancy and, hence, pulmonary flow might decrease. In a recent systematic review, cardiac output during pregnancy was significantly lower in women with heart disease and predicted a poor perinatal outcome (hypertension, pre-eclampsia, fetal growth restriction, stillbirth, and placental growth abruption).[20] However, although the poor pregnancy outcome may be a reflection of the limited cardiac output, it is also possible that other factors present in women with pre-existing heart disease may influence placental development, leading to poor pregnancy outcome. We found a high frequency of congenital heart disease in the newborn, which warrants further research.

Limitations

This registry, as with most other registries, has numerous limitations such as incomplete (<5%) and biased data. Specifically, the timing of diagnosis had not been reported in 25% of cases. This is a global registry with some centres having dedicated high-risk obstetric clinics and much higher volumes than others, which is likely to affect the outcome. In general, centres in ROPAC are typically tertiary centres with well-organized pregnancy clinics. Thus, all conclusions must be drawn with caution.

In addition, the diagnosis of PH was not made with heart catheterization in all patients. As highlighted by others,[15] many

patients had echocardiographic diagnosis of probable PH because an invasive test would neither be feasible nor indicated. The interpretation of our data must take into account that echocardiography as a diagnostic modality has limitations in PH.

This is a relatively large series of patients with PH, but mortality occurred in only a limited number of cases. Therefore, interpretation of mortality rates per subgroup should be done cautiously. In many countries, patients are unable to return for 6-month follow-up visits owing to financial constraints (e.g. having to pay for the clinic visit and all investigations, and transport to the hospital). As late (6-month) follow-up was only reported in about 50% of the patients, the number of late deaths is likely to have been underestimated. Therefore only limited conclusion can be drawn from these data.

Conclusion

Despite the advent of a number of therapeutic options for patients with PH, pregnancy remains a substantial risk and commonly leads to heart failure. Mortality remains high, particularly in women with iPAH (although there is a limited number of patients: 3/7, 43%). However, there are marked differences in the maternal and fetal outcome of women with iPAH, CHD-PAH, oPAH, and LHD-PH, which need to be highlighted and investigated further. Our data differ from previous systematic overviews and pooled cases series as we included all subgroups of PH, including a high number of LHD-PH. As most deaths occurred postpartum, women should be kept in hospital for at least a week after delivery and possibly longer, and be monitored for arrhythmia, heart failure, and uterine haemorrhage in particular. Vaginal delivery is usually the preferred mode of delivery. Before conception, women need to be counselled, not only about the risk to their health in the short and longer term, but also about the overall poor outcome for their children. However, if pregnancy occurs, close follow-up with a minimum of monthly visits and echocardiograms to screen for and treat right heart failure are essential. Larger, prospective, carefully conducted multicentre studies in patients with PH are required to determine the exact pregnancy-related risk, the role of supportive care and advanced PH therapy, as well as predictors of outcome for each subgroup.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. ROPAC Investigators.

Figure S1. Flowchart of inclusion.

Table S1. Pulmonary hypertension medication.

Table S2. Characteristics of patients with and without follow-up.

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