

Pregnancy and pulmonary hypertension

An exploratory analysis of risk factors and outcomes

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Abstract

Pregnancy is usually contraindicated in patients with pulmonary hypertension (PH). Risk factors associated with the outcome of this rare disease have not been specifically explored before.

Medical records were retrospectively reviewed to identify patients with coexisting PH and pregnancy or delivery at Peking Union Medical College Hospital between January 2009 and June 2018. Demographics, characteristics of PH and pregnancy, management and outcomes were analyzed.

Thirty-six pregnant women with PH were identified, including 30 cases in WHO group 1, 5 cases of group 2 and 1 case of group 4. Median pregnancy duration was 24 weeks. The overall maternal mortality rate was 8.3% (3/36), and the late fetal mortality was 31.6% (6/19). Pulmonary vascular-targeted medications were used in 17 of 26 patients with moderate or severe PH, but in none with mild PH. Maternal mortality was 2/15, 1/11, and 0 among women with severe, moderate, and mild PH, respectively. All deaths reported to be diagnosed of PH after pregnancy, and have New York Heart Association (NYHA) grades II to IV. Cesarean section was performed in 22 patients, and mortality was 3/16 among women receiving cesarean section with general anesthesia.

Maternal mortality is associated with PH classification, severity of PH, delayed diagnosis of PH, and NYHA classification. Regional anesthesia seems superior to general anesthesia for cesarean section.

Abbreviations: NYHA = New York Heart Association, PH = pulmonary hypertension, WHO = World Health Organization.

Keywords: cesarean section, delivery, pregnancy, pulmonary hypertension

1. Introduction

Pulmonary hypertension (PH) is a histopathological disorder characterized by an increase in the pressure of the pulmonary artery, pulmonary vein, or pulmonary capillaries, leading to debilitating symptoms and shortened life expectancy. The 2013 World Health Organization (WHO) updated PH classification and PH was categorized into 5 groups based on etiology: pulmonary artery hypertension, PH due to left heart disease, PH due to lung diseases and/or hypoxia, chronic thromboembolic PH, and PH with unclear multifactorial mechanisms.^[1] The prevalence of PH was reported to be 97 cases per million with a female-to-male ratio of 1.8. The age-standardized death rate ranges between 45 and 123 per million population.^[2]

Pregnancy causes hemodynamic, anatomic, and biochemical changes throughout the gestation, during delivery, and in the postpartum period, which can be intolerable for a woman with PH.^[3] Therefore, pregnancy in PH is contraindicated in practice

guidelines due to high maternal and fetal morbidity and mortality.^[2] Pregnancy can be complicated by PH because PH may be unknown before pregnancy; pregnancy may be unplanned, or some PH patients take the risk of pregnancy for social reasons. It is estimated that the prevalence of pregnancy complicated by PH is approximately 178 cases per million deliveries.^[4]

Pregnant women with PH are at increased risk of complications and death for both mothers and fetus. Maternal mortality rates in pregnant women with PH have been reported to be as high as 30% to 56%.^[5] Even after the wide use of pulmonary vascular-targeted medications, maternal mortality remains unexpectedly high. Due to the lack of prospective large-scale studies, many questions remain unknown. Thus, the study aimed to explore potential risk factors associated with maternal outcomes.

2. Methods

The front pages of medical records were reviewed to identify women who had coexisting PH and pregnancy during hospitalization. Based on the International Statistical Classification of Diseases and Related Health Problems Tenth Revision, patients were retrieved with diagnostic codes indicating PH and pregnancy or childbirth between January 2009 and June 2018. Paper medical records were reviewed, and a case was included if it met the clinical diagnostic criteria of PH which was confirmed by right heart catheterization or transthoracic echocardiography. If the results of right heart catheterization were available, PH was defined as a mean pulmonary artery pressure greater than 25 mm Hg; otherwise, it was defined as a pulmonary artery systolic pressure greater than 35 mm Hg measured by echocardiography. A mean pulmonary artery pressure value of 25 to 35 mm Hg,

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36 to 45 mm Hg, or greater than 45 mm Hg measured by right heart catheterization corresponded to the mild, moderate, or severe PH, respectively. Alternatively, a pulmonary artery systolic pressure value of 35 to 55 mm Hg, 56 to 75 mm Hg, or greater than 75 mm Hg measured by echocardiography corresponded to the mild, moderate, or severe PH, respectively.^[2,6]

For each patient, PH was clinically classified into one of the 5 groups according to 2013 WHO classification:^[1] group 1: pulmonary arterial hypertension that was idiopathic, heritable, drug and toxin induced, or associated with connective tissue disease, HIV infection, portal hypertension, congenital heart diseases, and schistosomiasis; group 2: PH due to left heart disease; group 3: PH due to lung diseases and/or hypoxia; group 4: chronic thromboembolic PH; group 5: PH with unclear multifactorial mechanisms. Information about the use of PH-targeted medication was collected.

Obstetric data collected in the study included gestational age and parity, pregnancy duration, delivery mode, anesthesia, maternal and fetal status, and cause of early termination. Furthermore, the occurrence of PH before or after the pregnancy was noted, and New York Heart Association (NYHA) functional classification prior to delivery was assessed.

All the procedures performed in this study involving human participants were in accordance with the ethical standards of the Ethics Committee of Peking Union Medical College Hospital (Reference Number: S-K354). Written or verbal informed consents were obtained from all individual participants or their families.

2.1. Statistical analysis

The distributions of variables were examined. For skewed data such as age and pregnancy duration, they were expressed as median. Categorical data were expressed as the number and percentage. Because of the small sample size, all analyses were descriptive, and statistical inference was not performed.

3. Results

Detailed information for every patient, including demographic characteristics, etiology, advanced medication for PH, obstetric characteristics, management and outcomes, is listed in Table 1.

3.1. Demographic characteristics and etiology

Thirty-six cases that had PH during pregnancy between 2009 and 2016 were identified and included in the study. Thirty cases (83.3%) were classified into WHO group 1, 5 cases (13.9%) in group 2, 1 case (2.8%) in group 4, and none in group 3 or 5.

The median age was 26 years (19–38 years). All patients fulfilled the echocardiographic definition of PH, and right heart catheterization was performed in 4 patients. With respect to the etiology for PH, connective tissue diseases including systemic lupus erythematosus, primary Sjogren syndrome, and mixed connective tissue disease accounted for half of the cases. Congenital heart disease was the second most common cause, followed by idiopathic and valve/myocardium disease. The distribution of severity and etiology for PH is illustrated in Figure 1.

3.2. Obstetric characteristics

Twenty-five (69.4%) of the 36 patients were nulliparous. All patients had abortion (< 24 weeks, n=17) or preterm delivery (24–36 weeks, n=19), and the median pregnancy duration was

24 weeks (6–36 weeks). More than half of the patients (20/36) underwent emergent delivery. Thirty-four pregnant patients (94.4%) terminated pregnancy because of uncontrolled PH or primary diseases, and only 2 cases (5.6%) terminated pregnancy because of fetal abnormality (intrauterine embryo damage or intrauterine fetal death). Vaginal delivery was performed in 14 patients (38.9%) with aborted fetus, including 5 patients who underwent induced labor, and 9 patients who underwent dilation and evacuation. Cesarean section was performed in 22 patients (61.1%), including 16 patients who received cesarean delivery under general anesthesia, and 6 patients under intraspinal anesthesia. Nineteen patients (52.8%) had pregnancy durations of more than 24 weeks, and all of them received cesarean section.

3.3. Management of PH

Most pregnant women (72.2%) did not have or did not know the presence of PH before pregnancy. Diuretics were used in 24 patients (66.7%), while anticoagulants were administered to 12 patients (33.3%). More patients in whom PH was diagnosed before pregnancy (6/10, 60%) took pulmonary vascular-targeted medications than those in whom PH was diagnosed during pregnancy (11/26, 42.3%). Among 17 women taking PH-targeted medications, a phosphodiesterase type 5 inhibitor, a prostaglandin I₂, and an endothelin-receptor antagonist were administered to 12 (70.6%), 9 (52.9%), and 7 (41.2%) patients, respectively. Nine patients (52.9%) were on 2 or more types of advanced medicines.

3.4. Outcomes

Maternal death was noted in 3 patients, resulting in a mortality rate of 8.3%. All of them died from uncontrolled PH and cardiorespiratory failure after surgery. All deaths occurred in women with PH in WHO group 1, with moderate or severe PH severity, and with NYHA grade of II to IV. None of the deaths reported to have PH before pregnancy, and 2 of them were treated with advanced medications for PH. One woman had primary Sjogren syndrome, and the other 2 patients had ventricular septal defect with Eisenmenger syndrome. Patients followed termination of pregnancy during 22 to 35 weeks of gestation. All of them were delivered by cesarean section under general anesthesia and died within a week after delivery. Vasopressors were employed during or after operation in 8 patients, leading to a mortality rate of 37.5% in women with unstable hemodynamics. Extracorporeal membrane oxygenation was used in 2 women, one of whom survived, while the other died 2 days after operation.

When other potential risk factors were assessed, one of the 3 deaths was anemic (hemoglobin < 100 g/L), comparable to 8 anemic patients among 33 survivors. None of the deaths reported to have chronic liver disease, chronic kidney disease, chronic lung disease, arrhythmia, infection, gestational diabetes, or thyroid disorder.

In 19 women with the pregnancy duration equal to or more than 24 weeks, 6 fetal deaths were noted, resulting in a late fetal mortality rate of 31.6%. The pregnancy duration of the 6 fetal deaths ranged from 24 weeks to 30 weeks.

Figure 2 shows the use of advanced medication and outcome of pregnancy across 3 different severities of PH. Advanced medication was used in 65.4% of pregnant women with moderate or severe PH, but in none of women with mild PH. Maternal mortality in pregnant women with moderate or severe

Table 1
Characteristics of 36 pregnant women with pulmonary hypertension.

Age	WHO PH group	Etiology	PH severity	PH therapy	NYHA prior delivery	PH before pregnancy	Parity	Pregnancy duration (wk)	Delivery timing	Delivery mode	Delivery Anesthesia	Maternal status	Fetal status
29	1	MCTD	Moderate	ERA, PDE5	II	Yes	G2P0	29	Emergent	CS	GA	Alive	Alive
21	1	SLE	Moderate	PDE5	II	No	G1P0	31	Emergent	CS	SA	Alive	Alive
23	1	SLE	Severe	PDE5	III	No	G1P0	23	Emergent	CS	CEA	Alive	Terminated
23	1	SLE	Moderate		I	No	G1P0	30	Emergent	CS	GA	Alive	Dead
24	1	SLE	Mild		IV	No	G1P0	32	Emergent	CS	GA	Alive	Alive
26	1	SLE	Mild		III	No	G1P0	35	Emergent	CS	GA	Alive	Alive
26	1	SLE	Moderate		III	No	G1P0	24	Emergent	CS	GA	Alive	Dead
27	1	SLE	Moderate	PDE5, PGI ₂	III	Yes	G2P0	10	Planned	TA (D&E)	GA	Alive	Terminated
28	1	SLE	Mild		I	No	G1P0	21	Planned	TA (IL)	GA	Alive	Terminated
29	1	SLE	Severe	PGI ₂	I	No	G2P0	31	Planned	CS	CEA	Alive	Alive
35	1	SLE	Moderate	PDE5, PGI ₂	IV	No	G2P1	15	Emergent	CS	GA	Alive	Terminated
28	1	CHD: ASD	Mild		II	No	G2P0	24	Planned	CS	GA	Alive	Dead
24	1	pSS	Moderate	PDE5	I	Yes	G3P1	6	Planned	TA (D&E)	GA	Alive	Terminated
27	1	pSS	Moderate	ERA	IV	No	G2P1	22	Planned	CS	GA	Dead	Terminated
29	1	pSS	Severe	ERA, PDE5	II	Yes	G2P1	12	Planned	TA (D&E)	LA	Alive	Terminated
29	1	pSS	Severe	ERA, PDE5, PGI ₂	III	No	G2P1	10	Emergent	TA (D&E)	GA	Alive	Terminated
23	1	Idiopathic	Severe	ERA, PGI ₂	II	Yes	G1P0	27	Emergent	CS	GA	Alive	Dead
25	1	Idiopathic	Severe	PDE5, PGI ₂	III	No	G2P0	33	Emergent	CS	GA	Alive	Alive
26	1	Idiopathic	Moderate		II	No	G1P0	35	Planned	CS	CEA	Alive	Alive
38	1	Idiopathic	Severe	PGI ₂	I	No	G4P0	32	Emergent	CS	GA	Alive	Alive
19	1	CHD: VSD (ES)	Severe		IV	No	G1P0	29	Planned	CS	GA	Dead	Dead
25	1	CHD: single atrium	Severe		IV	No	G1P0	30	Emergent	CS	CEA	Alive	Alive
30	1	CHD: ASD	Moderate	PDE5	I	Yes	G1P0	8	Emergent	TA (D&E)	GA	Alive	Terminated
22	1	CHD: VSD (ES)	Severe	PDE5, PGI ₂	II	No	G1P0	35	Planned	CS	GA	Dead	Alive
24	2	MR	Mild		II	No	G3P0	29	Emergent	CS	CSEA	Alive	Alive
31	2	RHD	Severe		III	No	G4P1	21	Emergent	TA (IL)	LA	Alive	Terminated
20	2	MR	Mild		I	Yes	G2P1	16	Planned	TA (IL)	LA	Alive	Terminated
22	2	AR, MR	Severe		III	No	G1P0	32	Planned	CS	GA	Alive	Alive
32	4	Pulmonary embolism	Mild		I	No	G4P2	11	Emergent	TA (D&E)	GA	Alive	Terminated
20	1	CHD: VSD (ES)	Severe		II	Yes	G1P0	15	Emergent	TA (IL)	LA	Alive	Terminated
25	1	SLE	Moderate		III	No	G1P0	23	Emergent	TA (IL)	LA	Alive	Terminated
34	1	SLE	Mild		II	Yes	G1P0	10	Planned	TA (D&E)	GA	Alive	Terminated
32	1	SLE	Severe	PDE5	II	No	G2P1	36	Emergent	CS	GA	Alive	Alive
26	1	Idiopathic	Severe	ERA, PGI ₂	III	No	G3P2	27	Planned	CS	GA	Alive	Dead
36	1	CHD: PDA	Mild		II	Yes	G5P1	11	Planned	TA (D&E)	GA	Alive	Terminated
34	2	Cardiomyopathy	Mild		III	No	G1P0	6	Planned	TA (D&E)	GA	Alive	Terminated

AR = atrial regurgitation, ASD = atrial septal defect, CEA = continuous epidural anesthesia, CHD = congenital heart disease, CS = cesarean section, CSEA = combined spinal-epidural anesthesia, D&E = dilation and evacuation, ERA = endothelin-receptor antagonist, ES = Eisenmenger syndrome, GA = general anesthesia, IL = induced labor, LA = local anesthesia, MCTD = mixed connective tissue disease, MR = mitral regurgitation, NYHA = New York heart association, PDA = patent ductus arteriosus, PDE5 = phosphodiesterase type 5 inhibitor, PGI₂ = prostaglandin I₂, PH = pulmonary hypertension, pSS = primary Sjogren syndrome, RHD = rheumatoid heart disease, SA = spinal anesthesia, SLE = systemic lupus erythematosus, TA = therapeutic abortion, VSD = ventricular septal defect, WHO = world health organization.

PH was 11.5%, but all women with mild PH survived. Abortion rate and late fetal mortality were similar in the 3 groups. Figure 3 shows the outcome of pregnant women with PH in WHO group 1. Women with congenital heart disease had the highest maternal mortality, women with connective tissue disease had the highest abortion rate, and women with idiopathic PAH had the highest late fetal mortality.

4. Discussion

In this retrospective study, we described maternal and fetal outcomes of 36 pregnant women with PH admitted to a tertiary hospital in the past 9 years. Similar to previous studies,^[4,7-9] patients in WHO group 1 accounted for the majority of the population in our study, probably attributable to the fact that pulmonary artery hypertension commonly affects women in childbearing age and pregnancy is most likely to occur in this subgroup of women.^[10] The novel finding of this study is that we find a few potential risk factors associated with maternal mortality.

Maternal mortality rates have been reported to be as high as 30% to 56% before the advent of advanced pulmonary vascular-targeted medications,^[5] but have declined to 5% to 25% in recent studies.^[4,6,8,9,11,12] About half of patients in this study were given PH-targeted advanced therapy. The maternal mortality of 8.3% is in the lower limit of the range, indicating an improved maternal outcome in nowadays. The median pregnancy duration in this study is shorter than that reported in studies with higher maternal mortality rates,^[4,9] which might partly explain the lower maternal mortality in our study. The late fetal mortality was 31.6% in the study, which was much higher than that reported in other studies (0%–18%).^[4,9,12-14] Because all women with PH in this study had preterm delivery, the high fetal mortality might also be attributable to the shorter median pregnancy duration in our study. Therefore, a short pregnancy duration favors a lower maternal mortality, but is unfavorable to the fetal outcome. However, due to the small number of patients, the association between pregnancy duration and maternal mortality was not found in our study.

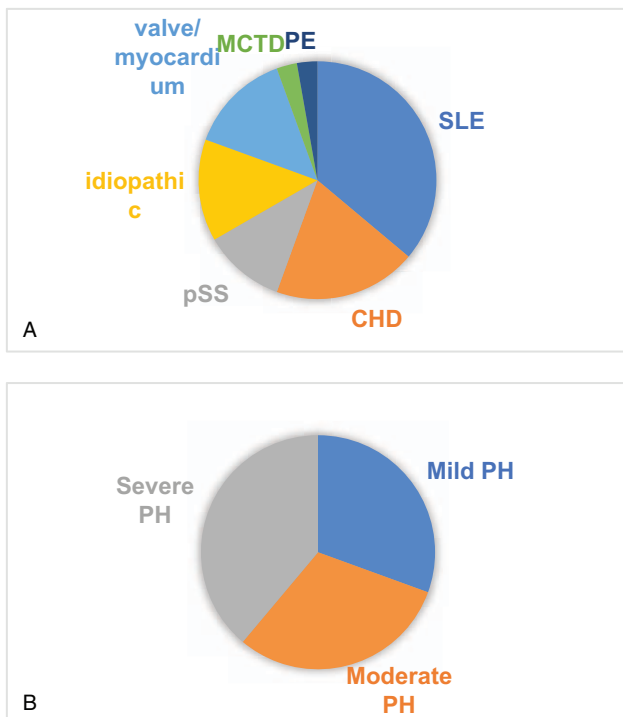


Figure 1. Distribution of etiology (A) and severity (B) for pulmonary hypertension. CHD=congenital heart disease, MCTD=mixed connective tissue disease, PE=pulmonary embolism, PH=pulmonary hypertension, pSS=primary Sjogren syndrome, SLE=systemic lupus erythematosus.

Pregnancy in PH is contraindicated in practice guidelines due to high maternal and fetal morbidity and mortality.^[2] Many patients with PH were recommended to terminate pregnancy early in this study. However, our study together with many other studies shows that maternal mortality is associated with the severity of PH.^[4,6,15] It is still controversial on whether pregnant

women with mild PH can be allowed to have children. Moreover, our study shows a higher maternal mortality in the subgroup of patients with congenital heart diseases (2/7) than those with connective tissue diseases (1/18) or idiopathic PH (0/5), indicating that maternal outcomes may be different in PH patients with different etiologies.

Impressively, PH was diagnosed before pregnancy in only around one-fourth of the pregnant women and none of them reported death. Therefore, screening for PH is necessary for pregnant women at high risks, especially those with connective tissue diseases or congenital heart diseases. The hypotensive shock was prominent during the first 72 hours postpartum; therefore, most maternal deaths occurred early after delivery.^[7,14,16,17] In our study, all the deaths occurred within 1 week after delivery, highlighting the importance of intensive care after delivery for high-risk patients.

Vaginal delivery will cause pain and increase intrathoracic pressures which may help to decrease venous return.^[3] Therefore, cesarean delivery between 34 and 36 weeks gestation is recommended as the preferred mode of delivery for pregnant women with PH by the Pulmonary Vascular Research Institute.^[18] In our study, because all deliveries were premature, vaginal delivery was used in only patients with aborted fetus, and all patients with gestational age of more than 24 weeks received cesarean section. However, there is no high-quality evidence on the optimal mode of delivery.^[4,8,17,19,20] Our study shows that cesarean section with epidural/spinal anesthesia has a lower mortality (0/6) than that with general anesthesia (3/16), which may be due to the less influence of regional anesthesia on hemodynamics. Similar results are reported in some previous studies. Therefore, cesarean delivery with regional anesthesia is recommended for pregnancy complicated by PH.^[9,18] But for patients with severe right heart failure, especially those with unstable hemodynamics, general anesthesia is usually unavoidable.

The power of the study was compromised by a limited number of enrolled cases because of rarity of the disease. As a result,

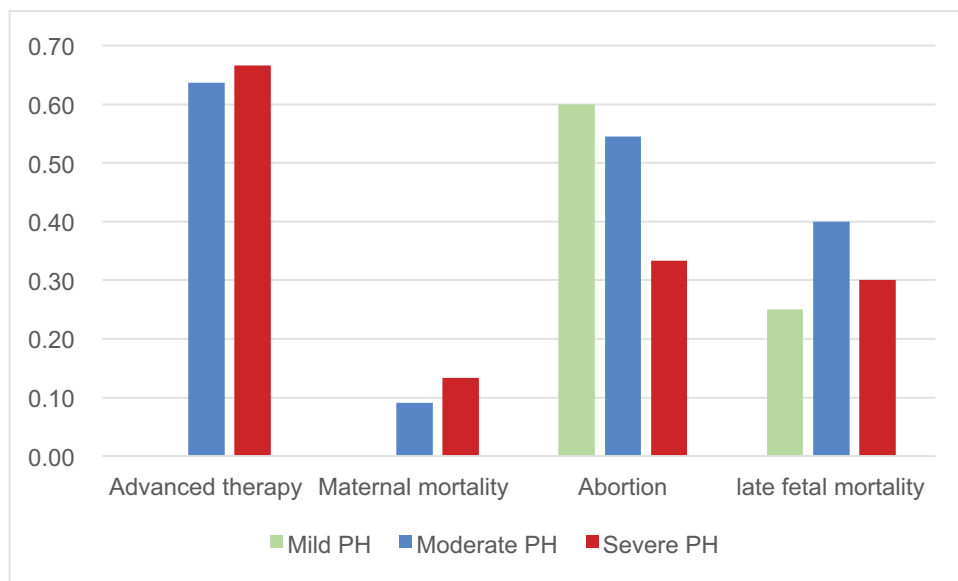


Figure 2. Outcome of pregnancy and different severities of pulmonary hypertension. *Abortion is defined as delivery less than 24 weeks, while late fetal mortality is defined as delivery more than 24 weeks. PH=pulmonary hypertension.

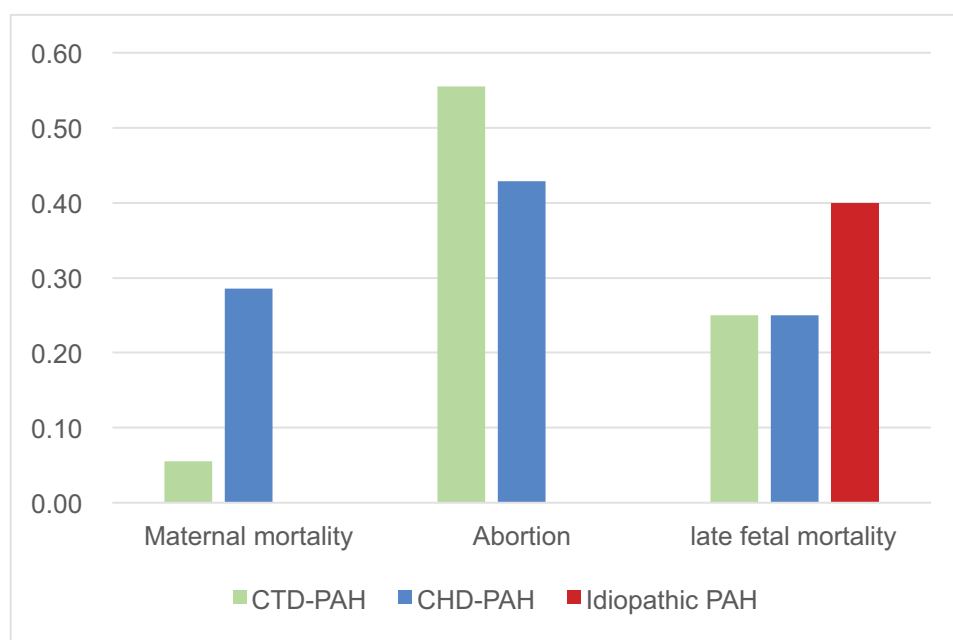


Figure 3. Outcome of pregnancy and different etiologies of pulmonary artery hypertension. *Abortion is defined as delivery less than 24 weeks, while late fetal mortality is defined as delivery more than 24 weeks. CHD=congenital heart disease, CTD=connective tissue disease, PAH=pulmonary artery hypertension.

statistical analysis was precluded. Still, this study demonstrated a few possible risk factors for maternal mortality, including moderate to severe PH, WHO group 1, delayed diagnosis of PH, NYHA grade II to IV, and general anesthesia. Patients with these risk factors should be referred to perinatal centers. Caring for this population with a multidisciplinary team is important and imperative. Only when a large registry database enrolling this group of patients becomes possible, high-quality evidence evaluating risk factors for the outcomes can be obtained.

In conclusion, we demonstrate a relatively low maternal mortality but a high late fetal mortality, which are probably attributable to a short median pregnancy duration. Maternal mortality is associated with PH classification, severity of PH, delayed diagnosis of PH, and NYHA classification. Regional anesthesia is superior to general anesthesia for cesarean section.

Author contributions

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