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.[4] 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,
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 echo-cardiography corresponded to the mild, moderate, or severe PH, respectively.²,³

For each patient, PH was clinically classified into one of the 5 groups according to 2013 WHO classification:¹¹ 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 that 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 | Anesthesia | Maternal status | Fetal status |
|-----|--------------|----------|-------------|------------|--------------------|---------------------|--------|------------------------|---------------|--------------|------------|----------------|-------------|
| 29  | 1            | MCTD     | Moderate    | ERA, PDE5  | II                 | Yes                 | G2P0   | 29                     | Emergent      | CS           | GA         | Alive         | Alive       |
| 27  | 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    | III        | No                  | G2P0   | 30                     | Emergent      | CS           | GA         | Alive         | Alive       |
| 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         | Alive       |
| 27  | 1            | SLE      | Moderate    | PDE5, PG12 | 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      | PG12       | I                   | No                  | G2P0   | 31                     | Planned CS    | CEA          | Alive       | Alive         | Alive       |
| 35  | 1            | SLE      | Moderate    | PDE5, PG12 | IV                 | No                  | G2P0   | 15                     | Emergent      | CS           | GA         | Alive Terminated |
| 28  | 1            | CHD: ASD | Mild        | II         | No                  | G2P0   | 24                     | Planned       | CS           | GA         | Alive         | Alive       |
| 24  | 1            | pSS      | Moderate    | PDE5       | I                   | Yes                 | G3P1   | 6                      | Planned       | TA (D&E)     | GA         | Alive Terminated |
| 27  | 1            | pSS      | Severe      | ERA, PDE5  | IV                 | No                  | G2P1   | 22                     | Planned       | CS           | GA         | Alive Terminated |
| 29  | 1            | pSS      | Severe      | ERA, PDE5  | II                  | Yes                 | G2P1   | 12                     | Planned       | TA (D&E)     | LA         | Alive Terminated |
| 29  | 1            | pSS      | Severe      | ERA, PDE5  | III                 | No                  | G2P1   | 10                     | Emergent      | TA (D&E)     | GA         | Alive Terminated |
| 23  | 1            | Idiopathic| Severe     | ERA, PG12  | II                  | Yes                 | G1P0   | 27                     | Emergent      | CS           | GA         | Alive         | Alive       |
| 25  | 1            | Idiopathic| Severe     | PDE5, PG12 | III                 | No                  | G2P0   | 33                     | Emergent      | CS           | GA         | Alive Terminated |
| 26  | 1            | Idiopathic| Moderate    | II         | No                  | G1P0   | 35                     | Planned CS    | CEA          | Alive       | Alive         | Alive       |
| 38  | 1            | Idiopathic| Severe     | PG12       | II                  | No                  | G4P0   | 32                     | Emergent      | CS           | GA         | Alive Terminated |
| 19  | 1            | CHD: VSD | Severe     | PDE5       | IV                 | No                  | G1P0   | 29                     | Planned CS    | CEA          | Alive       | Alive Terminated |
| 25  | 1            | CHD: single atrium | Severe | IV | No                  | G1P0   | 30                     | Emergent CEA  | CS         | Alive       | Alive Terminated |
| 30  | 1            | CHD: ASD | Moderate    | PDE5       | I                   | Yes                 | G1P0   | 8                      | Emergent       | TA (D&E)    | GA         | Alive Terminated |
| 22  | 1            | CHD: VSD | Severe     | PDE5, PG12 | 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      | II         | 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      | II         | No                  | G1P0   | 32                     | Planned CS    | GA         | Alive       | Alive         | Alive       |
| 34  | 4            | Pulmonary embolism | Mild  | I            | No                  | G4P2   | 11                     | Emergent | TA (D&E)     | GA         | Alive Terminated |
| 20  | 1            | CHD: VSD | 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, PG12  | III                 | No                  | G2P2   | 27                     | Planned CS    | GA         | Alive       | Alive       |
| 36  | 1            | CHD: PDA | Mild        | II         | Yes                 | G2P1   | 11                     | Planned       | TA (D&E)     | GA         | Alive Terminated |
| 34  | 2            | Cardiomyopathy | Mild  | II            | 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, **PG12** = prostaglandin I2, **PH** = pulmonary hypertension, **pSS** = primary Sjogren syndrome, **RHD** = rheumatoid heart disease, **SA** = spinal anesthesia, **SE** = 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, 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. 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, but have declined to 5% to 25% in recent studies. Because 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, 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%). 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.
Pregnancy in PH is contraindicated in practice guidelines due to high maternal and fetal morbidity and mortality. 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. 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. 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. 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. 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. 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. 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,
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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