

# General anesthesia is an independent predictor for worse maternal outcome in pregnant pulmonary arterial hypertension patients without cardiac shunt but not for those with shunt

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## Abstract

**Background:** Although pregnancy imposes extra risk in patients with pulmonary arterial hypertension (PAH), hemodynamic characteristics vary between PAH patients with and without cardiac shunts. However, previous studies did not take hemodynamic differences in PAH patients into consideration for pregnancy outcome analysis. We aimed to identify predictors for peripartum outcome of PAH patients without/with cardiac shunt.

**Methods:** We retrospectively analyzed the medical records of PAH gravidae parturied by cesarean delivery (C-section) from 4 hospitals. Maternal death and major adverse cardiac events (MACEs) occurring during pregnancy or within 6 weeks postpartum were defined as composite end points. Risk factors for end points were analyzed separately in patients with and without cardiac shunt. The effect of general anesthesia on MACEs and maternal death was analyzed considering cardiac shunts.

**Results:** One hundred and eighty-one PAH gravidae were included, of whom 85 had PAH without cardiac shunt and 96 with shunt. Patients who met combined end points were 19/85 in those without shunt compared with 23/96 in those with shunt. The mortality rates were 11.8% and 9.4%, respectively. Both World Health Organization functional class (WHO-FC) III/IV and general anesthesia were predictors for gravidae without shunt, whereas only WHO-FC III/IV was a predictor for gravidae with shunt. General anesthesia increased the MACE risk (odds ratio, 9.000; 95% confidence interval, 2.628–30.820) and maternal mortality (odds ratio, 11.000; 95% confidence interval, 2.595–46.622;  $P = 0.039$ ) in patients without cardiac shunt but not in those with shunt during C-section.

**Conclusion:** All PAH gravidae with WHO-FC III/IV are at high risk and should receive intensive care. General anesthesia should be avoided during C-section for PAH gravidae without a cardiac shunt.

**Keywords:** Cardiac shunt, Composite end points, Mortality, General anesthesia, Pregnancy, Pulmonary hypertension

The data sets generated during and/or analyzed during the current study are not publicly available because of privacy or ethical restrictions but are available from the corresponding author on reasonable request.

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## Introduction

Pulmonary arterial hypertension (PAH) is a progressive and debilitating disease characterized by occlusive pulmonary vascular remodeling and increased pulmonary vascular resistance (PVR), which eventually leads to right-sided heart failure and death. Pulmonary hypertension (PH) is clinically classified into 5 groups according to similar clinical presentation, pathological findings, hemodynamic characteristics, and treatment strategy.<sup>[1]</sup> Idiopathic PAH (IPAH), heritable PAH, PAH associated with connective tissue disease, HIV infection, portal hypertension, and congenital heart disease (CHD) all belong to group 1 PAH, according to the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines or the diagnosis and treatment of PH.<sup>[1]</sup> Normally, maternal organs undergo significant physiological alterations during pregnancy, with PVR decreased adaptively to increased cardiac output during pregnancy.<sup>[2–6]</sup> However, because of the lack of a physiologic decrease in PVR, pulmonary pressures rise along with the increased cardiac output, resulting in increased right ventricular strain and eventually in right ventricular failure in PAH patients.<sup>[7]</sup> The rate of maternal death in women with PAH can be as high as 30% to 50%.<sup>[8,9]</sup> As such, pregnancy is strongly discouraged in patients with PAH according to the ESC/ERS guidelines.

What is intriguing is that maternal mortality varies with different etiologies of PAH. Hemodynamic adaptation is quite different between PAH patients with or without cardiac shunt, especially during pregnancy. Li et al.<sup>[10]</sup> published the largest single-center experience of patients with CHD-PAH giving birth; the maternal mortality was 7.7%

in patients with postoperative CHD-PAH, whereas no maternal death occurred in CHD-PAH patients with left-to-right shunt, even though the PAH target therapy rate was as low as 33.3% in this group. A possible explanation is that the excessively increased afterload of the right side of the heart may partially be abated by right-to-left shunt through the defects in PAH patients with unrepaired CHDs but not in patients without cardiac shunt.

Although hemodynamic changes vary between the 2 subgroups, currently suggested risk predictors for PAH management do not distinguish PAH patients with from those without cardiac shunt because PAH is a relatively rare disease with low morbidity.<sup>[11,12]</sup> In the present study, we took hemodynamic differences in patients with PAH into consideration for pregnancy outcome analysis. We carried out a multicenter retrospective study in northern China to clarify the prenatal risk predictors for PAH gravidae considering cardiac shunt.

## Methods

### Study population

The medical records of all pregnant women with group 1 PAH who were managed to parturition or underwent therapeutic abortion by cesarean delivery (C-section) between October 2010 and August 2020 at Qilu Hospital of Shandong University, Shandong Provincial Hospital affiliated to Shandong First Medical University, Shandong Provincial Qianfoshan Hospital, and Affiliated Hospital of Qingdao University were reviewed retrospectively. All patients were diagnosed according to right-sided heart catheterization with mean pulmonary artery pressure  $\geq 25$  mmHg and pulmonary arterial wedge pressure  $\leq 15$  mmHg either before pregnancy or after delivery. We used the following exclusion criteria: (1) patients diagnosed only by echocardiography without catheterization data; (2) patients with group 2 (PH due to left heart disease), group 3 (PH due to lung diseases and/or hypoxia), or group 5 PAH (PH with unclear, multifactorial mechanisms, or both) according to the 2015 ESC guideline<sup>[13]</sup>; and (3) patients treated with therapeutic abortion within the first trimester. This research was approved by the steering committee of the Institutional Human Ethics Committee of Qilu Hospital (reference no. 2018-155; September 11, 2018) and was approved by the ethics committee at each participating center. Written informed consent was waived by the steering committee of the Institutional Human Ethics Committee of Qilu Hospital owing to the anonymized retrospective nature of the analysis.

### Study design

The included cases were divided into 2 cohorts according to the occurrence of composite maternal end points. The composite maternal end points included maternal death and major adverse cardiac events (MACEs) occurring during pregnancy or within 6 weeks postpartum. Major adverse cardiac events included the following conditions: deterioration of heart function (decline in World Health Organization [WHO] functional class, hypotension need for vasopressor, and cardiac shock), de novo arrhythmia (sustained or non-sustained symptomatic arrhythmia), and cardiac arrest. In patients with multiple events, only the first event was noted. For each patient, we also collected the following information: demographic characteristics, clinical classification of PAH, weeks of gestation, delivery mode, anesthesia options, choice of abortion, details of targeted therapies, WHO functional class (WHO-FC), serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), platelet count, activated partial thromboplastin time, prothrombin time, and estimated systolic pulmonary arterial pressure (sPAP) by echocardiography at admission. Severe PAH was defined as sPAP  $>70$  mmHg. The contraindications to epidural anesthesia,

including (1) shock and low blood volume; (2) infection at the puncture site or bacteremia and sepsis; and (3) coagulation problems, were also recorded.

### Statistical analysis

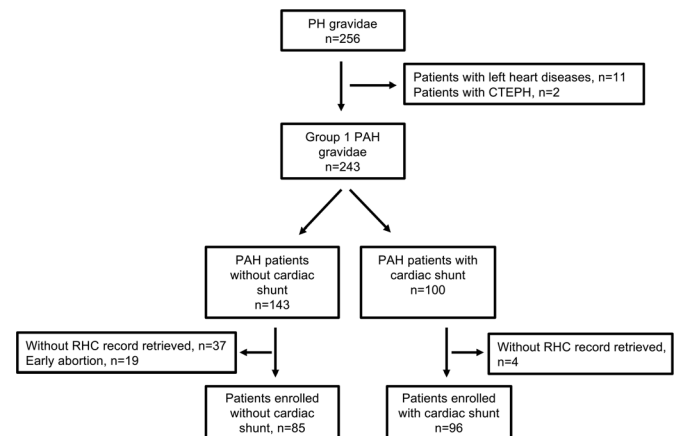
Analysis was performed with SPSS software version 13.0 (Armonk, New York, NY, USA). Continuous data are expressed as median (lower quartile, upper quartile) and were compared using Mann-Whitney U test. Categorical data are expressed as n, n(%) were compared using Fisher's exact test or Chi-square test where appropriate. Univariable logistic regression was used to identify clinical parameters associated with the composite end point during C-section; parameters significant on univariate analysis were included in a multivariate logistic regression model.  $P < 0.05$  was considered to be statistically significant.

## Results

### Baseline characteristics and pregnancy outcomes

A total of 181 pregnancies with PAH were included in the present study (Fig. 1). Eighty-five gravidae had PAH without a cardiac shunt. Twenty-eight of 85 had IPAH, 49 of 85 had postoperative PAH of CHD, and 8 of 85 had PAH associated with systemic lupus. Thirty-eight patients of 85 were nulliparous, and 32 of 85 were diagnosed with de novo PAH during pregnancy. Forty-five of 85 patients were WHO-FC III/IV at admission, 51 of 85 patients had sPAP greater than 70 mmHg, whereas only 24 of 85 patients were treated with PAH-targeted drugs. Fifteen of 85 patients had general anesthesia because of low platelet levels ( $<70 \times 10^9/L$ ) in 3, unstable hemodynamics in 7, and unknown reasons in 5. There were 77 living deliveries, 19 of 85 patients met combined end points, all of them had MACEs, and the mortality rate was 11.8%. Fourteen of 85 patients had deterioration of heart function, 3 of 85 had de novo symptomatic arrhythmia, and 2 of 85 had cardiac arrest. Postpartum hemorrhage/thromboembolism occurred in 9 patients.

Ninety-six gravidae had PAH associated with uncorrected CHDs with cardiac shunts. Forty-seven of 96 patients were nulliparous, and 57 of 96 were diagnosed with de novo PAH during pregnancy. Thirty-seven of 96 patients were WHO-FC III/IV at admission, 68 of



**Figure 1.** Study population and process of inclusion. CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right-sided heart catheterization.

**Table 1**  
**Demographic and Clinical Information of the Study Subjects With and Without Combined End Points**

	Without Cardiac Shunt			With Cardiac Shunt		
	End Points Free (n = 66)	End Points (n = 19)	P	End Points Free (n = 73)	End Points (n = 23)	P
Age, y	28.5 (25, 32)	28.0 (25, 32)	0.916	26 (22, 32)	26 (24, 31)	0.621
Weeks of gestation upon delivery	36 (33, 38)	35 (34, 38)	0.381	37 (33, 38)	36 (34, 38)	0.763
Nulliparous	28 (42.4%)	10 (52.6%)	0.430	42 (58.3%)	15 (65.2%)	0.630
PAH etiologies			0.033			—
Idiopathic PAH	18 (27.3%)	10 (52.6%)		—	—	
Postoperative CHD	43 (65.2%)	6 (31.6%)		—	—	
Connective tissue disease	5 (7.5%)	3 (15.8%)		—	—	
Unrepaired CHD	—	—		73 (100%)	23 (100%)	
PAH diagnosed de novo during pregnancy	21 (31.8%)	11 (57.9%)	0.059	37 (50.7%)	10 (43.5)	0.635
Targeted drug therapy	17 (25.8%)	7 (36.8%)	0.391	8 (11.0%)	4 (17.4%)	0.473
PDE5i	15	5		6	4	
PGIs	5	5		0	1	
ERA after delivery	2	4		4	2	
Combined therapy	5	4		2	2	
General anesthesia	6 (9.1%)	9 (47.4%)	0.001	15 (20.5%)	8 (34.8%)	0.173
WHO-FC III/IV	28 (42.4%)	17 (89.5%)	0.188	21 (56.8%)	16 (69.6%)	0.001
sPAP >70 mm Hg	37 (56.9%)	14 (73.7%)	0.286	49 (67.1%)	19 (82.6%)	0.194
sPAP, mm Hg	73 (59, 92)*	96 (71, 106)	0.010	78 (61, 100)	115 (71, 125)	0.001
NT-proBNP, pg/mL	258 (108, 745)*	589 (115, 2124)	0.202	240 (106, 761)	458 (367, 1257)	0.003

Data are n, n (%), or median (lower quartile, upper quartile). Continuous data are compared using Mann-Whitney U test. Categorical data are compared using Fisher's exact test or  $\chi^2$  test where appropriate. CHD, congenital heart disease; ERA, endothelial receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitors; PGI, parenteral prostacyclin analog; sPAP, systolic pulmonary arterial pressure; WHO-FC, World Health Organization functional class.

\*Some subjects had missing data in these items.

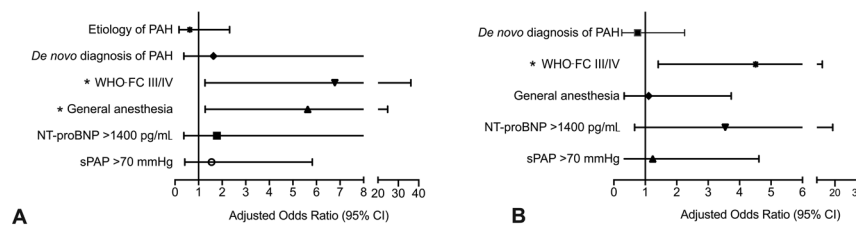
96 patients had sPAP greater than 70 mmHg, whereas only 12 of 96 patients were treated with PAH-targeted drugs. Twenty-three of 96 patients received general anesthesia because of low platelet levels ( $<70 \times 10^9/L$ ) in 8, unstable hemodynamics in 5, and unknown reasons in 10. There were 23 of 96 patients who met the combined end points, all of whom had MACEs, and the mortality rate was 9.4%. Seventeen of 96 patients had deterioration of heart function, 1 of 96 had de novo symptomatic arrhythmia, and 2 of 96 had cardiac arrest. Postpartum hemorrhage/thromboembolism occurred in 3 patients.

**Risk factors for maternal outcomes during C-section**

Risk factor analysis for maternal outcomes during C-section was performed. As shown in Table 1, we noticed that patients without cardiac shunt who met combined end points mostly had IPAH (10/19), worse cardiac function (WHO-FC III/IV 17/19 vs. 28/66,  $P < 0.001$ ) at admission, and higher percentage of general anesthesia

(9/19 vs. 6/66,  $P = 0.001$ ). There were no significant differences in age, weeks of gestation upon delivery, percentage of nulliparous women, de novo diagnosis of PAH during pregnancy, PAH target therapy treatment, and NT-proBNP level. Although sPAP was higher in the points group (96 [71, 106] vs. 73 [59, 92] mmHg,  $P = 0.010$ ), the percentage of severe PAH (sPAP >70 mmHg) was comparable (14/19 vs. 37/66,  $P = 0.286$ ). Etiology of PAH, WHO-FC III/IV, de novo diagnosis of PAH during pregnancy, general anesthesia, sPAP >70 mmHg, and NT-proBNP >1400 pg/mL were included in the multivariable logistic regression model. As shown in Fig. 2A, WHO-FC III/IV and general anesthesia remained significant, with odds ratios (ORs) of 6.68 (95% confidence interval [CI]: 1.272–36.150;  $P = 0.025$ ) and 5.63 (95% CI: 1.279–24.785;  $P = 0.022$ ), respectively.

Patients with cardiac shunt who met the combined end points had worse cardiac function (WHO-FC III/IV 16/23 vs. 21/73,



**Figure 2.** Results of multivariate analyses for maternal outcomes. (A) The strongest predictors of composite end points resulting from the present cohort without cardiac shunt were WHO-FC III/IV and general anesthesia. (B) The strongest predictors of composite end points resulting from the present cohort with cardiac shunt were WHO-FC III/IV. \* $P < 0.05$ . CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; sPAP, systolic pulmonary arterial pressure; WHO-FC, World Health Organization functional class.

$P = 0.001$ ), higher sPAP (115 [71, 125] vs. 78 [61, 100],  $P = 0.001$ ), and higher NT-proBNP levels (458 [367, 1257] vs. 240 [106, 761]  $P = 0.003$ ) at admission. There was no significant difference in age, weeks of gestation upon delivery, percentage of nulliparous women, de novo diagnosis of PAH during pregnancy, and PAH target therapy treatment. The percentage of severe PAH (sPAP >70 mmHg) was comparable (19/23 vs. 49/73,  $P = 0.194$ ). World Health Organization functional class III/IV, de novo diagnosis of PAH during pregnancy, general anesthesia, sPAP >70 mmHg, and NT-proBNP >1400 pg/mL were included in the multivariable logistic regression model. As shown in Figure 2B, only WHO-FC III/IV remained significant (OR: 4.509; 95% CI: 1.411–14.416;  $P = 0.011$ ).

### Comparison of general anesthesia on maternal MACEs and mortality between patients with or without cardiac shunt

To further compare whether cardiac shunt impose difference on maternal outcome in PAH patients who had general anesthesia, we carried out subgroup Chi-square analysis. As shown in Table 2, PAH patients who bares cardiac shunt had both lower MACE rate (26.1% vs. 60.0%,  $P = 0.037$ ) and maternal death (5.7% vs. 40.0%,  $P = 0.039$ ) compared to those who do not had cardiac shunt.

## Discussion

Pregnancy becomes a life-threatening condition when accompanied by PH. The maternal death rate has been reported to be as high as 30% to 56% in pregnancies with idiopathic PH before targeted therapy.<sup>[14]</sup> The total mortality of pregnant women with PH from the national inpatient database of the United States decreased to 0.8% from 2003 to 2012 compared with 3.3% in Europe because of careful and close monitoring by a multidisciplinary team.<sup>[15–17]</sup> To date, nationwide epidemiological data are still lacking in China; several retrospective studies showed that the mortality was 6.4% to 8.3%, and most cases are of PAH associated with unrepaired CHDs.<sup>[10,11]</sup> Maternal mortality was 17.6% in IPAH gravidae reported by another Chinese center<sup>[18]</sup> compared with 11.8% in the present study, indicating that PAH gravidae without cardiac shunt may be at a higher risk.

Pulmonary arterial hypertension-associated pregnancies are not entirely avoidable because a significant number of cases remain asymptomatic; thus, a diagnosis of PAH is not possible until cardiac function worsens during pregnancy.<sup>[10,19]</sup> Moreover, some early symptoms of PAH, such as moderate exertion dyspnea and peripheral edema, may be mistakenly interpreted as physiological consequences of pregnancy, leading to a delayed diagnosis of PAH.<sup>[10,19]</sup>

Several studies analyzed risk factors for complications during the prenatal period in patients with CHD and proved worse cardiac functional class before delivery to be an independent risk factor.<sup>[10,12]</sup> In the present study, we proved that for PAH gravidae without cardiac shunt, FC III/IV before delivery is a predictor for maternal MACEs and mortality.

Although both vaginal and cesarean deliveries are permitted by the American Heart Association for PAH in pregnancy,<sup>[20]</sup> C-section has been reported in most case series or studies. The application of anesthesia is extremely challenging in patients with PAH, especially general anesthesia. According to the 2015 ESC/ERS guidelines, although epidural is probably better tolerated than general anesthesia, it is still unclear which form of anesthesia is preferable.<sup>[11]</sup> General anesthesia is superior in circulatory and breathing control, but the increase in PVR caused by positive-pressure ventilation may lead to deterioration of right-sided heart function. Bedard et al.<sup>[21]</sup> noted that general anesthesia was associated with increased maternal mortality. However, general anesthesia tends to be applied in patients with severe right-sided heart failure because it is superior to regional anesthesia in terms of circulation and ventilation control, which may result in selective bias during analysis. In our previous study, which did not distinguish PAH gravidae with cardiac shunt from those without cardiac shunt, although the proportion of general anesthesia was much higher in PAH patients who had prenatal complications, it was not a prenatal risk factor for maternal MACEs or mortality after multivariate regression analysis.<sup>[22]</sup> Since January 1, 2010, there have been 9 articles focused on PAH gravidae in which the etiology, cardiac shunt, anesthesia method, maternal mortality, and/or MACEs in each individual subject were identifiable. There were 89 PAH gravidae without cardiac shunts in these studies. Thirty-four of 89 had general anesthesia, and the maternal mortality was 17.6% (6/34), whereas no death occurred in patients who had epidural or intraspinal anesthesia.<sup>[10,11,18,19,23–27]</sup> Studies focusing on CHD-PAH pregnancies did not conclude that general anesthesia is a risk factor for maternal outcomes either.<sup>[10,28]</sup> In a recent study by Luo et al.,<sup>[28]</sup> almost 35% of patients overall and 44% of patients with severe PAH received general anesthesia, but the overall maternal mortality decreased to as low as 4% in southern China, and the authors concluded that either epidural or general anesthesia contributed to promising outcomes. What we should notice is that in Luo and colleagues,<sup>[28]</sup> study, most patients had CHD-PAH with systemic to pulmonary shunt, and the hemodynamics are different in this subgroup compared with patients without shunt, which may alleviate the increased right-sided heart load caused by mechanical ventilation during general anesthesia. This may not be true in pregnancies without cardiac shunt, as discussed previously, because that elevated right-sided heart load could not be bypassed through defects. In the present study, we proved that general anesthesia is an independent risk factor for PAH gravidae without cardiac shunt but not for patients with cardiac shunt.

## Limitations

This study had several limitations. First, more reliable indicators such as right-sided heart catheterization data at the time of pregnancy are not available for the majority of patients. Instead, we used WHO-FC plus NT-proBNP as surrogate parameters to evaluate the severity of PAH in the different groups. Second, this was a retrospective observational study mainly focused on the delivery

**Table 2**  
Comparison of MACE and Maternal Death Between Patients With/Without Cardiac Shunt Who Had General Anesthesia

	With Cardiac Shunt (n = 23)	Without Cardiac Shunt (n = 15)	P
MACEs	6/23 (26.1%)	9/15 (60.0%)	0.037
Maternal death	2/23 (5.7%)	6/15 (40.0%)	0.039

MACEs, major adverse cardiac events.

period. In the future, a randomized comparative study is needed to further clarify the effect of general anesthesia on prenatal mortality in PAH gravidae without cardiac shunts.

## Conclusion

This study innovatively considered the hemodynamic differences in PAH patients for pregnancy outcome analysis. This is the largest cohort focused on PAH gravidae without cardiac shunts. In summary, PAH patients should be well educated about the risks of pregnancy, especially those without cardiac shunts. In case of pregnancy, patients with WHO-FC III/IV should have intensive care to improve cardiac function, and general anesthesia should be avoided during C-section in PAH gravidae without a cardiac shunt.

## Conflict of interest statement

The authors declare no conflict of interest.

## Author contributions

Cui X was involved in study conceptualization, data curation and interpretation, and manuscript writing, revision, and final approval; Li M, Ji F, and Li G were involved in data collection and interpretation; Feng H, Qie L, and Ling M were involved in data interpretation and formal analysis; Ji Q was involved in data collection, interpretation, validation, and formal analysis; Jiang F was involved in data interpretation, data validation, formal analysis, and manuscript writing; Lu W was involved in study conceptualization, data collection, formal analysis, manuscript writing, and final approval.

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## Ethical approval of studies and informed consent

This study followed the principles of the Declaration of Helsinki as revised in 2013. The ethics approval of the study was approved by the steering committee of Institutional Human Ethics Committee of Qilu Hospital (reference no. 2018-155; September 11, 2018) and was approved by the ethics committee at each participating center. Written informed consent was waived by the steering committee of Institutional Human Ethics Committee of Qilu Hospital owing to the anonymized retrospective nature of the analysis.

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