

Long-term outcomes of pregnant women with pulmonary hypertension diagnosed by echocardiography: a retrospective cohort study in a single center from China

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Abstract

Recent studies suggest that pregnancy may not be absolutely contraindicated in women with moderate pulmonary hypertension. We aimed to evaluate the long-term outcomes of pregnant women with pulmonary hypertension diagnosed by echocardiography in our clinical department. Pregnant women with pulmonary hypertension, diagnosed by a pulmonary systolic arterial pressure > 30 mmHg via echocardiography, who were admitted in our department for termination of pregnancy or delivery between 2004 and 2016 were included in this retrospective cohort study. Demographic characteristics, clinical histories, perinatal outcomes, and follow-up outcomes after discharge were reported. The primary outcome was survival of the pregnant women after discharge. A total of 88 pregnant women with pulmonary hypertension were included in this cohort study. The women were categorized into severe and moderate pulmonary hypertension groups according to their pulmonary systolic arterial pressure at admission. Women with severe pulmonary hypertension were significantly more likely to have deteriorated cardiac function and higher incidence of neonatal complications during the perinatal periods ($p < 0.05$). During a median follow-up of 26 months, the mortality rate was significantly higher in women with severe pulmonary hypertension ($p < 0.05$). However, the accumulated survival rate was >90% for women with moderate pulmonary hypertension within the follow-up period. Multivariate Cox regression analyses showed that poor cardiac function before pregnancy, irregular antenatal care, and hyperuricemia were independent mortality risk factors for women with pulmonary hypertension after discharge. In conclusion, the long-term survival of pregnant women with moderate pulmonary hypertension diagnosed by echocardiography was considered acceptable in this cohort. Our findings suggest that pregnancy might not be absolutely contraindicated in women with moderate pulmonary hypertension.

Keywords

pulmonary hypertension, pregnancy, mortality, long-term, retrospective cohort

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Introduction

Pulmonary hypertension (PH) is a clinical syndrome characterized by progressively increasing pulmonary arterial pressure and right heart overload.¹ According to the World Health Organization (WHO) classification, PH etiologies are categorized into five groups: primary PH, PH caused by left heart diseases, PH caused by chronic lung diseases, PH caused by thrombo-embolization diseases,

and PH caused by other multifactorial diseases.² Patients with PH are characterized by symptoms of hypoxia and right heart failure, as evidenced by manifestations of

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cyanosis, exercise intolerance, and edema, all of which increase the risk of premature death.¹ Epidemiological studies showed that PH is more prevalent in women, particularly for those who are in younger childbearing ages.¹ Pregnancy is associated with significant hemodynamic changes, which may deteriorate cardiac function in women who have potential cardiac disorders.^{3,4} For women with PH, deterioration of cardiac function resulting from hemodynamic changes is dramatic following delivery.^{3,4} These women are likely to suffer from acute pulmonary and cardiac failure with the progression of pregnancy, which can result in both maternal and fetal mortality. Indeed, the mortality rate in pregnant women with PH was reported to be as high as 60%.⁵ Therefore, pregnancy has been absolutely contraindicated based upon current guidelines.^{6–8}

PH treatment strategies have advanced over the past decades, particularly with the application of targeted medications, such as prostacyclin receptor agonists, prostanoids, and type 5 phosphodiesterase inhibitors.^{9,10} As a result, life expectancies of patients with PH have been extended. Although PH in pregnant women is rare in developed countries, probably as a result of optimized health-care management, some women are at risk for developing PH prior to pregnancy. Early studies consistently showed that the mortality risk was dramatically higher for women with PH who became pregnant; however, some recent studies suggest that the pregnancy outcomes have improved, particularly for those with moderate PH treated with targeted PH medications.^{11–13} These findings highlight the possibility that pregnancy may not necessarily be contraindicated for women with moderate PH. Due to the limited cases of pregnant women with PH, long-term outcomes have been rarely reported. In this study, we aimed to retrospectively analyze the follow-up outcomes of pregnant women with PH diagnosed by echocardiography who attended our department for termination of pregnancy or delivery during 2004 to 2016.

Materials and methods

Patients and ethics approval

This study was designed as a single-center retrospective cohort study aiming to evaluate the long-term outcomes of pregnant women with PH diagnosed by echocardiography after discharge. Accordingly, medical charts for women with PH diagnosed by echocardiography who were admitted in the Department of Obstetrics in our hospital between November, 2004 and September, 2016 for delivery or termination of pregnancy were included and retrospectively analyzed. The study protocols were approved by the Ethics Committee of our institution before enrollment of any individual patient, and written consent forms were obtained from either each included patient or a patient's first-degree relative before study inclusion. Discharged patients who were unable to be contacted were excluded from analysis.

Diagnostic criteria and definitions of clinical parameters

Diagnosis of PH was based on the estimation of pulmonary systolic arterial pressure (PSAP) via echocardiography analyses. In brief, echocardiography was performed by experienced physicians when the patients were admitted. According to the Bernoulli equation, the tricuspid transvalvular pressure was estimated based on the velocities of tricuspid regurgitation blood flow.¹⁴ With no evidence of outflow obstruction of the right ventricles (RV), PSAP was estimated as the sum of tricuspid transvalvular pressure and right atrial pressure (RAP).¹⁴ RAP was estimated as 5 mmHg in most cases. However, RAP was estimated as 10 mmHg if significant inferior vena cava dilatation was observed and as 15 mmHg if significant clinical manifestations of right heart failure were observed, such as distention of jugular vein, ascites, and severe edema of the lower extremities.¹⁴ A diagnosis of PH was confirmed if the PSAP was >30 mmHg.¹ Patients were categorized as moderate PH (PSAP <50 mmHg) and severe PH (PSAP ≥50 mmHg) according to the echocardiography results at admission.¹ Other demographic and clinical characteristics, such as resting heart rate (HR), systolic and diastolic blood pressure (SBP and DBP, respectively), gestational week, percutaneous oxygen saturation, parameters of echocardiography examinations, levels of cardiac biomarkers (N-terminal pro-B type natriuretic peptide (NT-proBNP)), and other serum biochemical parameters including uric acids were obtained from medical charts at admission. Medical histories of the included patients were also abstracted to gather information regarding cardiac function as evaluated by the standard of the New York Heart Association (NYHA) before pregnancy and at admission.¹⁵ Medications used for PH treatment and related symptoms of heart failure were categorized as basic medications including diuretics, digoxin, cedilanid, sodium nitropruside, and metoprolol, and targeted medications including sildenafil, tadalafil, and bosentan before and during hospitalization.⁹ Regular formal antenatal care was defined as the scheduled access to obstetric examination according to the instructed standard of China. We also obtained data regarding delivery methods and anesthetic strategies for each of the included patients.

Outcomes

The primary outcome of our study was survival at follow-up correlated with PH after discharge according to the severity of PH diagnosed by echocardiography at admission. Other maternal and neonatal outcomes during the perinatal periods were also analyzed. Maternal outcomes included changes in NYHA cardiac classification at admission before pregnancy and at follow-up compared to after delivery. Deterioration of NYHA cardiac classification was defined as any increment in NYHA classification for the same woman. Incidences of obstetrical complications during the perinatal periods, including pregnancy-induced

hypertension (PIH), gestational diabetes mellitus, intrahepatic cholestasis, premature rupture of membranes, polyhydramnios, oligohydramnios, placental abruption, threatened uterine rupture, threatened premature delivery, anemia, and postpartum hemorrhage were also recorded. Neonatal complications, including premature infant, fetal growth restriction, fetal distress, fetal malformation, and stillbirth were also recorded. For premature neonates (gestational age (GA) < 36 weeks), neonates with asphyxia, and small for GA infants, admission and transfer to the pediatric department were indicated.

Statistical analyses

Continuous variables are summarized as means and standard deviations, while categorized variables are presented as numbers and proportions. The Student's t test was used for comparisons between two groups of continuous variables if they were normally distributed; otherwise, the Mann-Whitney U test was applied. For categorized variables, the Chi-square test was applied. We used the Kaplan-Meier survival analysis to evaluate the potential influence of PH severity diagnosed by echocardiography on survival of the pregnant women with PH after discharge. A multivariable Cox regression model was used to identify the predictors of

mortality for pregnant women with PH after discharge. Age, antenatal care, NYHA classification before pregnancy, resting HR, blood oxygen saturation (SpO₂), SBP and DBP, gestational week, baseline echocardiography parameters (left ventricular ejection fraction, and dimensions of RV), NT-proBNP and uric acid at admission, methods of anesthesia, and methods of delivery were included in the model. A p-value < 0.05 was considered statistically significant. We used the SPSS 19.0 software package for the above statistical analyses.

Results

Patient characteristics

Overall, 88 pregnant women with PH diagnosed by echocardiography who were admitted in our department between November, 2004 and September, 2016 for delivery or termination of pregnancy were included in the follow-up study. The follow-up was performed in December 2016. The follow-up durations varied from 3 to 103 months, with a median of 26 months. The baseline characteristics of the included patients, according to PH severity diagnosed by echocardiography at admission, are shown in Table 1. Pregnant women with moderate or severe PH were

Table 1. Baseline characteristics of pregnant women according to PH severity diagnosed by echocardiography.

Parameters	Moderate PH (n = 39)	Severe PH (n = 49)	p values
Mean age (years)	28.6 ± 6.3	28.1 ± 5.7	0.690
Resting HR (bpm)	95.0 ± 15.8	98.9 ± 16.0	0.255
Systolic blood pressure (mmHg)	117 ± 16	113 ± 19	0.458
Diastolic blood pressure (mmHg)	72 ± 11	69 ± 14	0.294
Gestational week at admission	38.0	34.4	0.021
SPO ₂ (%) at admission	98.0	96.0	0.003
NT-proBNP (pg/ml)	185	238	0.210
Uric acids (umol/L)	305.1	330.8	0.046
<i>Etiologies of PH</i>			
CHD	22 (56.4)	37 (75.5)	
RHD	13 (33.3)	10 (20.4)	
Hyperthyroidism	1 (2.6)	0 (0.0)	
SLE	1 (2.6)	0 (0.0)	
PIH	2 (5.1)	2 (4.1)	0.205
Cardiac surgeries before pregnancy	9 (23.1)	10 (20.4)	0.091
Antenatal consulting	4 (10.3)	5 (10.2)	1.000
Regular antenatal care	13 (33.3)	7 (14.3)	0.034
Primiparous	29 (74.4)	36 (73.5)	0.925
Users of basic medications ¹	14 (35.9)	27 (69.2)	0.073
Users of targeted medications ²	3 (6.1)	16 (41.0)	0.005

HR: heart rate; NT-proBNP: N-terminal pro-B type natriuretic peptide; PH: pulmonary artery hypertension; CHD: congenital heart disease; RHD: rheumatoid heart disease; SLE: systemic lupus erythematosus; PIH: pregnancy-induced hypertension.

¹Basic medications for PH include diuretics, digoxin, cedilanid, sodium nitroprusside, and metoprolol.

²Targeted medications for PH include sildenafil, tadalafil, and bosentan.

Table 2. Maternal and fetal characteristics and outcomes of women with PH diagnosed by echocardiography.

Parameters	Moderate PH (n = 39)	Severe PH (n = 49)	p values
Maternal characteristics			
Method of delivery			
Cesarean section	33	35	
Induction of labor via vagina	2	5	
Caesarean abortion	2	5	
Artificial abortion	2	4	0.655
Anesthesia			
Non-anesthetic	2	5	
Subarachnoid anesthesia	5	6	
Epidural anesthesia	8	9	
General anesthesia	23	29	
Local anesthesia	1	0	0.830
Obstetrical complications	14	10	0.105
Length of ICU stay (days)	2.0	3.0	0.083
Length of hospital stay (days)	7.0	7.0	0.618
Gestational week at delivery	37.6 ± 2.1	36.1 ± 3.1	0.019
Fetal outcomes			
Birth weight (g)	2976 ± 624	2403 ± 771	0.001
Fetal complications	3	18	0.001
Neonates with asphyxia (%)	23	18	0.124
Living birth (%)	100	94.3	0.493
Neonatal transfer to PD (%)	12.1	52.9	<0.001

ICU: intensive care unit; PD: pediatric department.

comparable with regard to age, resting HR, SBP and DBP, gestational weeks, SpO₂, NT-proBNP, and uric acids at admission (all p values > 0.05, Table 1). With regard to PH etiology, most women had PH that was associated with congenital heart disease (CHD) or rheumatoid heart disease (RHD), while some rare causes of PH, such as systematic lupus erythematosus (SLE), hyperthyroidism, or PIH, were also included. The proportions of primiparous women were similar between the two groups (p > 0.05), while pregnant women with severe PH diagnosed by echocardiography were less likely to have regular formal antenatal care, but more likely to use targeted medications for PH (p = 0.034 and 0.005, respectively, Table 1).

Maternal and fetal characteristics and outcomes

As shown in Table 2, the patterns for termination of pregnancies and the methods of deliveries, as well as the anesthetic strategies, were similar between the women with moderate and severe PH diagnosed by echocardiography (both p > 0.05). The maternal outcomes for women with moderate and severe PH, such as incidence of obstetrical complications and lengths of hospitalization and intensive care unit (ICU) stay, were comparable. There were 14 women with obstetric complication in the moderate PH

group (3 cases of preeclampsia, 4 cases of premature rupture of membranes, 2 cases of placental abruption, 4 cases of preterm birth, 1 case of polyhydramnios, 3 cases of gestational diabetes mellitus, and 1 case of postpartum hemorrhage) and 10 cases in the severe PH group (6 cases of preeclampsia, 2 cases of premature rupture of membranes, 1 case of polyhydramnios, 1 case of oligohydramnios, 1 case of gestational diabetes mellitus, and 2 cases of anemia). Some women had more than one obstetric complication simultaneously. Women with severe PH diagnosed by echocardiography had significantly shorter gestational weeks at delivery compared to those with moderate PH (p = 0.019). Moreover, neonatal birthweight was significantly lower and incidences of neonatal complications were significantly higher in women with severe PH diagnosed by echocardiography compared to those with moderate PH (both p = 0.001). Accordingly, neonates of women with severe PH were significantly more likely to be transferred to the pediatric department (p < 0.001).

Changes in cardiac classification during the perinatal period and within follow-up in women with PH

The distributions of NYHA classification for women with PH diagnosed by echocardiography before pregnancy, at

Table 3. Changes in maternal NYHA cardiac functional classification during the perinatal periods for women with PH diagnosed by echocardiography.

Parameters	Moderate PH (n = 39)		Severe PH (n = 49)		p
	n	%	n	%	
Before pregnancy					
I	27	69.2	25	51.0	0.069
II	12	30.8	22	44.9	
III	0	0.0	2	4.1	
At admission					
I	11	28.9	6	12.2	0.002
II	19	48.7	17	34.7	
III	9	23.7	18	36.7	
IV	0	0.0	8	16.4	
After delivery					
I	11	28.2	6	12.2	0.002
II	22	56.4	20	40.8	
III	5	12.8	17	34.7	
IV	1	2.6	6	12.2	
End of follow-up					
I	17	43.6	13	26.5	0.003
II	19	48.7	17	34.7	
III	2	5.1	6	12.2	
IV	1	2.6	13	26.5	
Deteriorated at admission	21	53.8	37	75.5	0.033
Deteriorated at follow-up	13	33.3	30	61.2	0.009

NYHA: New York Heart Association; PH: pulmonary hypertension.

admission, after delivery, and during follow-up are summarized in Table 3. Overall, women with severe PH diagnosed by echocardiography were associated with higher NYHA cardiac classification compared to those with moderate PH at the same periods ($p=0.069$, 0.002 , 0.002 , and 0.003 , respectively). Moreover, women with severe PH diagnosed by echocardiography were more likely to have deterioration in NYHA cardiac classification at admission compared to before pregnancy and during follow-up compared to women with moderate PH after delivery ($p=0.033$ and 0.099 , respectively).

Long-term outcomes of pregnant women with PH

The survival outcomes of discharged women with PH, according to PH severity diagnosed by echocardiography at admission, are shown in Fig. 1. As shown in the Kaplan–Meier survival analysis, women with severe PH diagnosed by echocardiography had significantly lower survival rates compared to those with moderate PH after discharge ($p=0.001$). The predicted survival rates for women with severe PH were 85.4%, 72.7%, and 35.0%, and for women with moderate PH were 97.0%, 96.0%, and

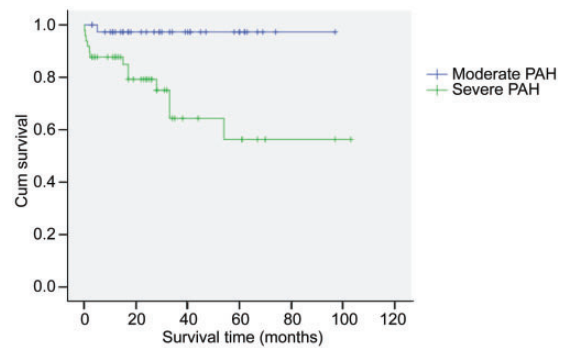


Fig. 1. Kaplan–Meier survival analysis curve for pregnant women with PH diagnosed by echocardiography according to PH severity.

90.0%, respectively. Result of multivariate Cox regression analyses showed that worse NYHA cardiac classification before pregnancy (for Class I: odds ratio (OR)=21.02, 95% confidence interval (CI): 2.75–160.64; for Class II: OR=236.08, 95% CI: 7.68–7262.81), irregular antenatal care (OR=37.02, 95% CI: 1.72–795.99), and hyperuricemia at admission (OR=1.013, 95% CI: 1.006–1.021) were independent predictors of mortality risk for women with PH diagnosed by echocardiography after discharge (Table 4).

Discussion

In this retrospective follow-up study of pregnant women with PH diagnosed by echocardiography in our department, we found that women with severe PH (PSAP at admission ≥ 50 mmHg) diagnosed by echocardiography had significantly worse maternal and neonatal outcomes during the perinatal periods compared to women with moderate PH (PSAP at admission between 30 and 49 mmHg). More importantly, we found that women with severe PH diagnosed by echocardiography had lower long-term survival rates after discharge (cumulative five-year survival of 35%), while women with moderate PH had acceptable long-term survival rates (cumulative five-year survival of 90%). Interestingly, results of the multivariate regression analyses showed that worse cardiac function, poor antenatal care, and hyperuricemia are potential independent predictors of mortality in pregnant women with PH diagnosed by echocardiography after discharge. Taken together, these results suggest that pregnancy should be contraindicated for women with severe PH diagnosed by echocardiography as they have significantly poor maternal and neonatal outcomes. Our findings also suggest that pregnancy might not be absolutely contraindicated in women with moderate PH.

Early observations consistently indicated that pregnancies in women with PH are associated with significantly increased maternal and neonatal mortality risk. Accordingly, current guidelines recommend that pregnancy should be absolutely contraindicated for women with PH. However, recent cohort studies have challenged this recommendation, particularly for those women who are receiving

Table 4. Multivariate Cox regression analyses of the mortality risk of pregnant women with PH diagnosed by echocardiography during follow-up.

Variables	B	SE	Wald	p	OR	95% CI for OR
NYHA class before pregnancy (compared with Class I)						
Class II	3.045	1.038	8.612	0.003	21.017	2.750–160.640
Class III	5.464	1.748	9.770	0.002	236.077	7.674–7262.812
Irregular antenatal care	3.611	1.565	5.322	0.021	37.016	1.721–795.993
Hyperuricemia	0.013	0.004	12.958	<0.001	1.013	1.006–1.021

Note: Variables in the Cox regression model included age, antenatal care, NYHA classification before pregnancy, resting HR, SpO₂, blood pressure, gestational age, baseline echocardiological parameters (left ventricular ejection fraction and dimensions of right ventricle), NT-proBNP, uric acid at admission, methods of anesthesia, and methods of delivery. NYHA: New York Heart Association; OR: odds ratio; CI: confidence interval; SE: standard error.

targeted medications for PH.^{11–13} In a European registry of 151 pregnant women with PH, the authors found that mortality in this group of patients with various forms of PH was lower than previously reported, with a maternal mortality rate of 3.3% within one week after delivery.¹² The authors attributed this lower than expected maternal mortality risk to specialized treatment of PH during pregnancy and delivery.¹² In another small-scale cohort of 20 women with PH that resulted from CHD, only a 5% maternal mortality was reported with no neonatal death, despite the high incidences of maternal heart failure events and neonatal complications.¹¹ The authors therefore cautiously advised that women with PH should not become pregnant.¹¹ In a recent report from India, which included 81 pregnancies in 73 women with PH and 80.8% PH caused by CHD, maternal mortality occurred in 5.4% patients, which was significantly lower than expected.¹³ The authors concluded that intensive multidisciplinary team management and active administration of novel targeted medications for PH significantly improved maternal outcomes, even in low- to middle-income countries with limited resources.¹³ Although these results shed some lights on the potential improvements of the prognosis for pregnant women with PH, there are some studies that have reported unaffected high maternal and neonatal mortality even with contemporary PH management. A retrospective study in the US including 49 cases of pregnant women with PH showed a 16% in-hospital maternal mortality rate,¹⁶ which was consistent with a 25% in-hospital incidence of adverse cardiovascular events reported from another US study based on the national inpatient samples of PH women.¹⁷

Although inconsistencies remain regarding in-hospital maternal and neonatal outcomes in pregnant women with PH, long-term outcomes after discharge in these patients have been rarely reported. To the best of our knowledge, only one single-center retrospective follow-up study was reported in Beijing, China. In this study, 110 pregnant women with PH caused by CHD were included; eight women suffered in-hospital mortality (7.3%), and only one

woman died within subsequent follow-up after puerperium.¹⁸ Results of our study expand the above findings by showing that within a follow-up duration of up to 108 months after discharge, women with severe PH had a cumulative five-year survival of 35%, while for women with moderate PH, the long-term survival rates seemed to be acceptable, with a cumulative five-year survival of 90%. Consistent with these findings, our study also showed that for women with severe PH diagnosed by echocardiography, pregnancy should be absolutely contraindicated, while for those with moderate PH, pregnancy might not be absolutely contraindicated.

Our Cox multivariate regression analyses also showed that baseline cardiac function and access to formal antenatal care are important factors that affect the long-term mortality risk of pregnant women with PH diagnosed by echocardiography. Our findings highlight the importance of extensive multidisciplinary team management for women with PH, particularly for pregnant women. Collaborative care, including expert cardiologists, obstetrics, and emergent medicine care, for pregnant women with PH may lead to effective treatment and intensive monitoring of this patient population, leading to improved outcomes. Evaluation of baseline cardiac function is significant for risk stratification in these women; pregnancy should be strictly avoided in women with PH with poor baseline cardiac classification. Interestingly, we also found that baseline hyperuricemia is a potential independent predictor of long-term mortality in pregnant women with PH diagnosed by echocardiography after discharge. Recent studies consistently showed that serum uric acid levels correlate with PH severity, and hyperuricemia may be an independent predictor of clinical prognosis in PH patients.^{19–21} The underlying mechanisms for the association between hyperuricemia and PH severity and prognosis could be attributed to potential oxidative stress-related injuries to the endothelium,²² which may lead to endothelial dysfunction and worsening PH severity.

Our study has limitations that should be considered when interpreting our results. Firstly, this was a single-center

retrospective study. Additional bias may exist compared to prospective cohort studies, and the results should be confirmed in prospective cohort and multiple-center studies. Secondly, no patients with Group I PH were included in this cohort, which may have skewed the results. Thirdly, the use of targeted PH medications, particularly after discharge, was not included in our current analyses since the information regarding PH treatment was difficult to obtain for our cohort. Moreover, no included patient underwent a right heart catheterization (RHC) procedure; therefore, all PH diagnoses were based on an estimation of PSAP via echocardiography analyses. In addition, some of the included patients were treated with PH-directed therapy, although PH-directed therapy without an RHC is not recommended by European or US guidelines. Use of targeted PH medications in PH patients due to left heart disease should optimally be based on the results of measuring combined post-capillary and pre-capillary pulmonary hypertension (CpcPH) with RHC.²³ However, because RHC examination may expose pregnant women to X-rays and possibly adversely affect the fetus, none of the included women received RHC examination. Our decision to use targeted medications was mainly based on the recommendations of the Chinese²⁴ and Japanese²⁵ guidelines for managing PH, supporting the rationale for using targeted medications in patients with NYHA class \geq II. In addition, we only included five women with PH caused by left heart diseases, such as gestational hypertension or hyperthyroidism. These may further contribute to the bias of the analysis. Moreover, the results of our multivariate regression analyses should be cautiously interpreted since the sample size of the study was limited and the CI ranges of our outcome data were wide. Finally, in view of the observational nature of our study, we can only state that the long-term survival rates seemed to be acceptable for women with moderate PH. Thus, we do not suggest that current recommendations for women with PH should be changed based solely on our findings.

In conclusion, the long-term survival for pregnant women with moderate PH diagnosed by echocardiography seemed to be acceptable in this study cohort. As such, results of our study suggest that pregnancy might not be absolutely contraindicated in women with moderate PH. However, due to the limitations of our small-scale single-center retrospective cohort study design, large-scale cohort studies with evidenced-based management in women with PH diagnosed by RHC are needed to confirm these findings. Extensive multidisciplinary team management for pregnant women with PH might be important to improve clinical outcomes.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics approval

The study protocols were approved by the Ethics Committee of our institution before enrollment of any individual patient. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written consent forms were obtained from either each included patient or a patient's first-degree relative before study inclusion.

Guarantor

YD.

Contributorship

WL: Project development, Data analysis, Manuscript writing. YD: Data collection, Data analysis, Manuscript writing. LW: Data collection. All authors revised, read, and approved the final manuscript.

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