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RESEARCH ARTICLE

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Maternal and fetal outcomes of pregnant women with pulmonary arterial hypertension associated with congenital heart disease in Beijing, China: A retrospective study

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Abstract

As pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) may increase maternal and fetal risk, this study explored the pregnancy outcomes of Chinese women with PAH-CHD. The clinical data of pregnant women with PAH-CHD admitted to the Beijing Anzhen Hospital from 2010 to 2019 were retrospectively analyzed; these patients and their offspring were followed up, with a mean period of 5.9 ± 2.7 years. Overall, 260 patients with PAH-CHD were included. The mean maternal age was 27.7 ± 4.1 years, and 205 (78.8%) patients were nulliparous. The estimated systolic pulmonary artery pressure was 40–50 mmHg in 34.6% of the patients, 50–70 mmHg in 23.1%, and >70 mmHg in 42.3%. More than 96% of patients were diagnosed with PAH-CHD before pregnancy. During pregnancy, heart failure occurred in 19.2% of the patients. Cesarean delivery was performed in 88.1% (15.0% emergency) of the patients. Complications included fetal distress (5.8%), preterm delivery (34.2%), and low birth weight (33.8%). A total of 15 mothers (5.8%) died, with the highest mortality rate in those with Eisenmenger syndrome (10/43, 23.3%), and 10 offspring died (3.8%), two (0.8%) following hospital discharge and eight (3.1%) while in hospital. Although most pregnant women with PAH-CHD were able to have children, PAH increased the maternal and fetal risk. Thus, an individualized risk-based approach with shared decision-making may be more appropriate in pregnant women with PAH-CHD.

KEYWORDS
Eisenmenger syndrome, low birth weight, pregnancy, preterm delivery

INTRODUCTION

Pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) is a pathophysiological disorder that involves multiple clinical conditions and can complicate most cardiovascular and respiratory diseases. Increased pulmonary blood flow through a left-to-right shunt has been recognized to trigger molecular and cellular changes in the pulmonary vasculature, leading to progressive PAH.[1] Pregnancy of women with PAH-CHD is associated with additional risks, and the recent practice guidelines of the European Society of Cardiology and the American College of Cardiology/American Heart Association strongly discourage pregnancy in these patients.[2,3] However, pregnancy is a major life event for most women, and some women with PAH still want and have the right to give birth. These women are willing to disregard the objections of their family and doctors and risk their own health to realize their dream of motherhood.[4,5] This patient population, therefore, warrants special attention.

According to the data from the Registry of Pregnancy and Cardiac Disease of the European Society of Cardiology, pregnancy risk and fetal outcome remain paramount. How to reduce the risk and avoid the deaths of pregnant women with PAH remains to be explored. As the PAH landscape changes and patients are living longer with a better quality of life, knowledge of the management of PAH in pregnant women increases. Although studies have been conducted on pregnant women with PAH, studies focusing on treatment are limited.[6] Patient counseling and management rely on case series and observational studies from various centers with fluctuating treatment modalities over time.[7] This study aimed to compare and analyze the complications and outcomes of pregnant women with PAH in each subtype group. Our findings contribute new insights for the clinical management of pregnant women with PAH-CHD.[8]

METHODS

Study design and setting

In 2007, the Beijing Anzhen Hospital was designated as the only referral and consultation center for pregnant patients with heart diseases in Beijing. Almost all pregnant women with heart disease in Beijing visit this hospital for consultation and treatment; there are many pregnant women with PAH.

This study retrospectively analyzed the clinical data of 260 patients with PAH-CHD who were admitted to our hospital between January 2010 and December 2019. Patients who gave birth in our hospital with a mean pulmonary artery pressure (mPAP) >20 mmHg diagnosed by right heart catheterization were included in this study. Those who gave birth in another hospital or did not meet the diagnostic criteria for PAH were excluded.

We divided the pregnant women with PAH-CHD into the following groups, based on the proceedings of the Cologne Consensus Conference 2018: left-to-right shunt (L-R-PAH), Eisenmenger syndrome (ES-PAH), patients with repaired defects (repaired-PAH), and PAH associated with a coincidental small defect of CHD (sd-PAH).[9] We analyzed the differences in the study variables between these groups. Furthermore, patients were divided into three groups based on their sPAP values as follows: mild (40–50 mmHg), moderate (50–70 mmHg), and severe (>70 mmHg). As the mothers and offspring were followed up, we analyzed their outcomes. Data were collected on age, heart failure (HF), death, use of general anesthesia, birth weight, pre-eclampsia, placental abruption, fetal distress, and other events, such as arrhythmia and growth restriction.

Definitions

Abortion was defined as termination of pregnancy before 28 weeks, preterm birth was defined as induced labor and termination of pregnancy at 29–36 weeks, and full-term pregnancy was defined as birth after 37 weeks. Babies with a birth weight of <2500 g were defined as having low-birth-weight (LBW). The cardiac function grade of the patients was divided into four Grades, I–IV, according to the New York Heart Association cardiac function grade. Pulmonary hypertensive crisis (PHC) was defined based on pulmonary hypertension, a rapid sharp increase in pulmonary artery pressure in a short period, approaching or exceeding systemic circulation pressure and aortic pressure due to a variety of factors, resulting in severe hypocardiac output (cardiac output <3.5 L/min), hypoxemia (arterial oxygen partial pressure <60 mmHg), hypotension (blood pressure <90/60 mmHg), and acidosis (pH <7.35).

Statistical analysis

Baseline characteristics and cardiac, obstetric, and fetal outcomes were collected for the PAH-CHD group. We compared the baseline characteristics and outcomes of PAH in the L-R-PAH, ES-PAH, repaired-PAH, and sd-PAH groups. Categorical data are presented as frequencies and percentages, and chi-square tests were used for comparisons. The normality of continuous data was confirmed using Kolmogorov–Smirnov tests, and continuous data are presented as the mean ± standard

deviation or median and first and third quartiles (Q1–Q3), as appropriate. Differences between the groups, such as age, were assessed using Student's t tests. We used one-way analysis of variance to determine whether there is a difference in the population mean represented by multiple sample means. Cox regression analysis was used to analyze the effects of various factors on survival. Two-sided $p < 0.05$ were considered statistically significant. All analyses were performed using SPSS (version 26.0; SPSS Inc.) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria, 2021).

RESULTS

Characteristics of study participants

A total of 19,822 deliveries were performed at the Beijing Anzhen Hospital from January 1, 2010 to December 31, 2019. Data were collected on 260 pregnant women with PAH-CHD comprising 141 L-R-PAHs, 43 ES-PAHs, 62 repaired-PAHs, and 14 sd-PAHs (Figure 1). The baseline characteristics of the patients are presented in Table 1.

Analysis of complications

In patients with PAH-CHD, the incidence rates of maternal death, HF, PHC, preterm delivery, and infants with LBW were 5.8%, 19.2%, 5.8%, 34.2%, and 33.8% respectively. There were significant differences in maternal death, pre-eclampsia, HF, and PHC among the PAH subgroups. The incidence rates of PHC, HF, hypertension, and pre-eclampsia were significantly higher in the ES-PAH group than in the other groups ($p < 0.05$); that of arrhythmia was relatively high in all groups, with no significant difference among the PAH groups. More details are shown in Table 1.

Cox regression analysis was performed for heart failure, length of hospital stay, gestational week, cesarean delivery, age, and treatment for pulmonary hypertension. We found that in patients with high pulmonary hypertension, heart failure was a risk factor, whereas treatment and cesarean delivery served as protective factors.

Management of PAH-CHD

Diuretics were prescribed to 71 patients (27.3%) during pregnancy, and digoxin to 51 patients (19.6%). Depending on PAH severity, at least one targeted drug was prescribed to reduce PAH, including sildenafil, tadalafil, ventavis, remodulin, and even nitric oxide. According to cardiac function, the drugs prescribed included dopamine, dobutamine, epinephrine, norepinephrine, milrinone, pituitrin, and levosimendan. Extracorporeal membrane oxygenation was used postoperatively in three cases because of PHC and HF. However, all three patients died due to multiple organ failure. Only two patients (0.8%) had embolism events; thus, the use of anticoagulant drugs did not significantly affect patient outcomes.

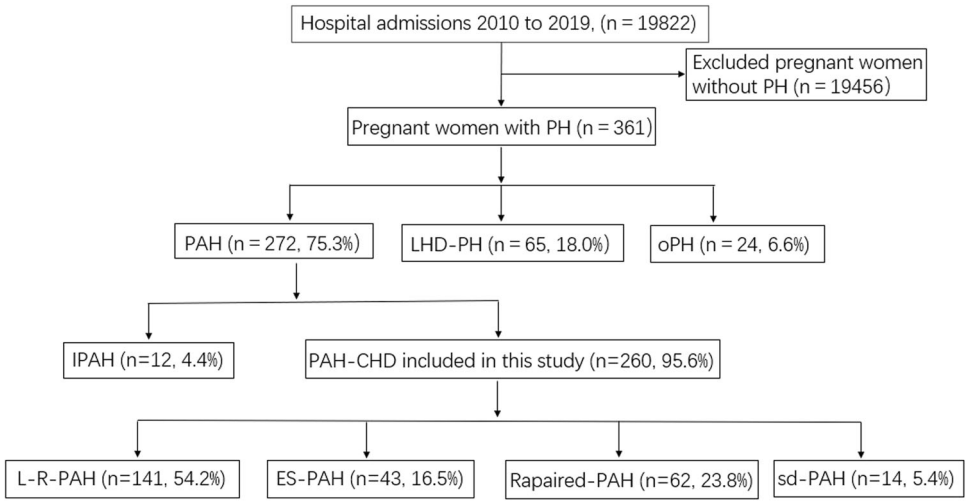

FIGURE 1 Flowchart of inclusion and exclusion of the study participants. ES-PAH, pulmonary hypertension in Eisenmenger syndrome; IPAH, idiopathic pulmonary hypertension; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PH, pulmonary hypertension; LHD-PH, pulmonary hypertension associated with left heart disease; L-R-PAH, left to right shunt pulmonary arterial hypertension; oPH, pulmonary hypertension due to other diseases; sd-PAH, small defect accompanied by pulmonary hypertension

TABLE 1 Baseline characteristics, management, and outcomes of pregnant women with PAH-CHD ($N = 260$)

	Total	L-R-PAH ($n = 141$, 54.2%)	ES-PAH ($n = 43$, 16.5%)	Repaired-PAH ($n = 62$, 23.8%)	sd-PAH ($n = 14$, 5.4%)	*p*
Characteristics						
Age, years, mean ± SD	27.7 ± 4.1	28.1 ± 4.1	26.7 ± 4.0	27.1 ± 4.0	27.4 ± 4.6	0.185
Nulliparous	205 (78.8)	97 (68.8)	39 (90.7)	55 (88.7)	11 (78.6)	0.003
Diagnosis						0.303
Before pregnancy	251 (96.5)	133 (94.3)	42 (97.7)	62 (100.0)	14 (100.0)	
During pregnancy	9 (3.5)	8 (5.7)	1 (2.3)	0 (0.0)	0 (0.0)	
NYHA class						<0.001
I	25 (9.6)	23 (16.3)	0 (0.0)	2 (3.2)	0 (0.0)	
II	139 (53.5)	97 (68.8)	10 (23.3)	29 (46.8)	2 (14.3)	
III	66 (25.4)	16 (6.2)	17 (39.5)	25 (40.3)	8 (57.1)	
IV	30 (11.5)	4 (2.8)	16 (37.2)	6 (9.7)	4 (28.6)	
sPAP						<0.001
40–50	90 (34.6)	70 (49.6)	0 (0.0)	19 (30.6)	1 (7.1)	
50–70	60 (23.1)	41 (29.1)	3 (7.0)	13 (21.0)	3 (21.4)	
70	110 (42.3)	30 (21.3)	40 (93.0)	30 (48.4)	10 (71.4)	
Mode of delivery						0.104
Vaginal	26 (10.0)	20 (14.2)	1 (2.3)	5 (8.1)	0 (0.0)	<0.001
CS	229 (88.1)	119 (84.4)	42 (97.7)	54 (87.1)	14 (100.0)	<0.001
Emergency CS	39 (15.0)	12 (8.5)	15 (34.9)	7 (11.3)	5 (35.7)	0.001
General anesthesia	3 (1.2)	0 (0.0)	2 (4.7)	1 (1.6)	0 (0.0)	0.196
Outcome						
PHC	15 (5.8)	2 (1.4)	10 (23.3)	2 (3.2)	1 (7.1)	<0.001
Maternal death	15 (5.8)					<0.001
Postpartum (<1 week)	1 (0.4)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	
Postpartum (>1 week to <6 months)	11 (4.2)	1 (0.7)	7 (16.3)	2 (3.2)	1 (7.1)	
Postpartum (>6 months)	3 (1.2)	0 (0.0)	2 (4.7)	0 (0.0)	1 (7.1)	
Other complications						
Heart failure	50 (19.2)	20 (14.2)	16 (37.2)	11 (17.7)	3 (21.4)	<0.001
Postpartum hemorrhage	35 (13.5)	19 (13.5)	6 (14.0)	8 (12.9)	2 (14.3)	0.285
Arrhythmology	44 (16.9)	22 (15.6)	7 (16.3)	11 (17.7)	4 (28.6)	0.113
Hypertension	14 (5.4)	6 (4.3)	5 (11.6)	3 (4.8)	0 (0.0)	0.734
Placenta previa	7 (2.7)	3 (2.1)	3 (7.0)	1 (1.6)	0 (0.0)	0.685
Pre-eclampsia	43 (16.5)	19 (13.5)	12 (27.9)	11 (17.7)	1 (7.1)	0.001
Gestational diabetes	32 (12.3)	22 (15.6)	5 (11.6)	5 (8.1)	0 (0.0)	0.263
Fetal distress	13 (5.0)	7 (5.0)	3 (7.0)	3 (4.8)	0 (0.0)	0.796
Growth restriction	8 (3.1)	4 (2.8)	2 (4.7)	2 (3.2)	0 (0.0)	<0.001

Note: Values are presented as *n* (%), unless otherwise indicated.

Abbreviations: ES-PAH, pulmonary arterial hypertension associated with congenital heart disease that progressed to Eisenmenger syndrome; LBW: low-birth weight; L-R-PAH, pulmonary arterial hypertension associated with left-to-right shunt congenital heart disease; NYHA, New York Heart Association; oPAH, pulmonary arterial hypertension associated with other congenital heart disease; PHC, pulmonary hypertensive crisis; sd-PAH: pulmonary arterial hypertension associated with small defects of congenital heart disease.

Regarding PAH-specific medication, 37.2% of the patients did not use any targeted drugs, as they had relatively mild cases of PAH; 29.8% were treated with monotherapy (sildenafil); 24.6% with dual drug therapy (sildenafil and treprostinil); and 8.4% with triple therapy (sildenafil, treprostinil, and bosentan; considering that bosentan may affect the normal development of the fetus, it is generally not administered during pregnancy but can be administered after birth).

Maternal outcomes

Hospitalization was required in 249 (95.8%) patients, 89 (34.2%) of whom were admitted more than once. Admission of 102 (39.2%) patients was for cardiac reasons, and 15 mothers died (5.8%) (Table 1).

The ES-PAH group showed the highest mortality (10/43, 23.3%). There were 14 patients (14/15, 93.3%) with New York Heart Association cardiac function grades of III–IV before delivery, and 13 patient deaths (13/15, 86.7%) were related to HF, PHC, and multiple organ failure. The details of maternal mortality are presented in supplemental materials. The classification of various pulmonary arterial hypertension associated with congenital heart disease are presented in supplemental materials. Figure 2 shows the outcomes of pregnancy with different levels of sPAP. There were significant differences in the events of HF, preterm delivery, LBW, and miscarriage.

Delivery

Most deliveries were cesarean (CS; 229, 88.1%), 221 (85.0%) for cardiac reasons, and 39 (15.0%) were emergency deliveries. Seven (2.7%) patients underwent general anesthesia for CS deliveries. The anesthesia methods used for other patients included epidural, spinal, combined epidural, and local anesthesia.

The incidence of preterm delivery (83.7%), infants with LBW (83.7%), general anesthesia during CS (4.7%), HF (34.9%) and PHC (23.3%), and maternal death (23.3%) were higher in the ES-PAH group than in the L-R-PAH, repaired-PAH, and sd-PAH groups. Additional details are presented in Table 1.

Fetal and neonatal outcomes

A total of 10 offspring died, eight in the hospital and two outside the hospital. All offspring who died were premature, underdeveloped, and had LBW, and the causes of death were related to these factors. Among them, one infant born at 29 weeks had a birth weight of 645 g, one died later due to lung disease, one had

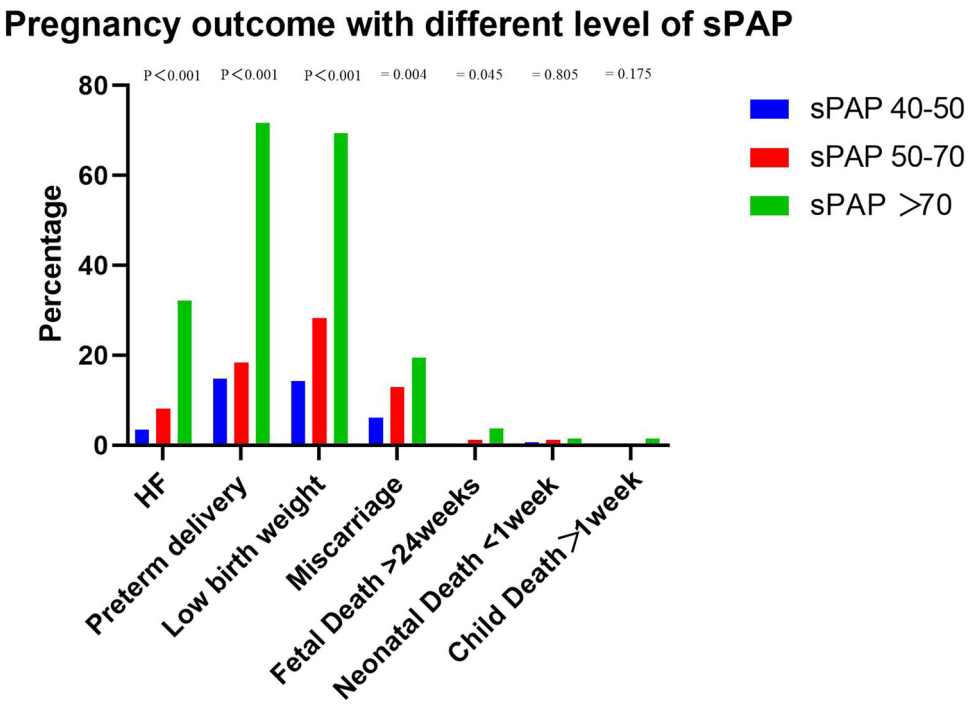

FIGURE 2 Pregnancy outcomes of the study participants stratified by sPAP levels. HF, heart failure; sPAP, systolic pulmonary arterial hypertension.

multiple malformations, and two were stillborn. Of the 15 mothers and 10 children who died, five cases included the death of both children and mothers.

Five offspring had CHD (two with ventricular septal defect, one with both ventricular and atrial septal defects, one with patent foramen ovale, and one with patent ductus arteriosus). Details of the fetal and neonatal outcomes are presented in Table 2.

Follow-up data

A total of 224 (86.2%) patients with PAH were followed up, with a mean follow-up period of 5.9 ± 2.7 years. Three (1.3%) mothers died, six (2.7%) had symptoms of cardiac insufficiency, 36 (16.1%) received targeted drugs to reduce PH, 41 (18.3%) had limited activity, and 43 (19.2%) had arrhythmia.

Two offspring (0.9%) died after discharge. There was a high incidence of preterm birth and LBW among all infants. A high proportion of newborn infants required continued treatment, and problems regarding slow growth and development at the beginning of life were observed. However, the growth and development of most offspring did not differ significantly from their peers, with only two (0.9%) showing delayed growth and development. Five (2.2%) of the offspring had CHD, one had a closed patent foramen ovale, one had a recovered patent ductus arteriosus, and one was under observation for ventricular septal defect. The other offspring with CHD were treated with surgery (see Table 3).

TABLE 3 Follow-up data on mothers ($n = 224$) and offspring ($n = 224$)

	n (%)	
Mothers		
Death	3	1.3
Targeted therapy	36	16.1
Limited activity	41	18.3
Symptoms of cardiac insufficiency	6	2.7
Arrhythmology	43	19.2
Offspring		
Death	2	0.9
Congenital heart disease	5	2.2
Growth and development lag behind	2	0.9
CHD of offspring	5	2.2

Abbreviation: CHD, congenital heart disease.

TABLE 2 Fetal and neonatal outcomes

Fetal complications	PAH-CHD 260 (72.0)	L-R-PAH 141 (54.2)	ES-PAH 43 (16.5)	Repaired-PAH 62 (23.8)	sd-PAH 14 (5.4)	*p* value
Median gestational weeks	35.5 ± 3.1	36.5 ± 2.9	31.4 ± 2.5	34.9 ± 3.2	32.8 ± 2.1	<0.001
Premature delivery	89 (34.2)	23 (16.3)	36 (83.7)	21 (33.9)	9 (64.3)	0.002
Mean newborn weight	2667.6 ± 657.5	2902.6 ± 461.8	2083.2 ± 748.2	2507.9 ± 561.5	2437.7 ± 553.3	0.001
Total LBW (<2500 g)	88 (33.8)	10 (7.1)	36 (83.7)	31 (50.0)	11 (78.6)	0.009
LBW (1500–2500 g)	73 (28.1)	9 (6.4)	23 (53.5)	30 (48.4)	11 (78.6)	
VLBW (1000–1500 g)	14 (5.4)	1 (0.7)	12 (27.9)	1 (1.6)	0 (0.0)	
ELBW (<1000 g)	1 (0.4)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	
Mortality	10 (3.8)	2 (1.4)	7 (16.3)	1 (1.6)	0 (0.0)	0.018
Fetal mortality, >24 weeks	5 (1.9)	0 (0.0)	5 (11.6)	0 (0.0)	0 (0.0)	0.177
Neonatal mortality, <1 week	3 (1.2)	1 (0.7)	2 (4.7)	0 (0.0)	0 (0.0)	0.912
Neonatal mortality, >1 week	2 (0.8)	1 (0.7)	0 (0.0)	1 (1.6)	0 (0.0)	0.854
Fetal distress	15 (5.8)	2 (1.4)	11 (25.6)	1 (1.6)	1 (7.1)	0.880
Fetal growth restriction	5 (1.9)	1 (0.7)	3 (7.0)	0 (0.0)	1 (7.1)	0.265
Premature rupture of membranes	14 (5.4)	4 (2.8)	9 (20.9)	1 (1.6)	0 (0.0)	0.746
Miscarriage, <24 weeks	13 (5.0)	4 (2.8)	6 (14.0)	2 (3.2)	0 (0.0)	0.043
CHD	7 (2.7)	4 (2.8)	1 (2.3)	1 (1.6)	1 (7.1)	0.362

Abbreviations: CHD, congenital heart disease; ELBW, extremely low birth weight; ES-PAH, pulmonary arterial hypertension associated with Eisenmenger syndrome; LBW, low birth weight; L-R-PAH, L-R-PAH, pulmonary arterial hypertension associated with left-to-right shunt congenital heart disease; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; VLBW, very low birth weight.

DISCUSSION

Through our study, we revealed that in China, PAH-CHD increases the risks associated with childbirth; however, most patients were able to have children. The perinatal period of pregnant women with PAH is associated with problems, such as premature delivery, LBW, and rescue. The offspring of women with PAH face risks of developmental retardation, growth restriction, and other problems in their early lives.

Maternal death (5.8%) in our study cohort occurred at a much higher rate than that observed in healthy people (the maternal mortality rate among healthy people in Beijing is approximately 0.01%). Mortality in our study was similar to or lower than that previously reported.[10] This may be because our hospital specialized in pregnant patients with cardiac diseases; hence our "pregnancy team" was experienced, and some deaths were avoided. In addition, in the patient group with an sPAP ranging from 40 to 50 mmHg, there were only a few cases of very mild PAP.

The mortality rate found in this study was similar to that reported by Ladouceur et al. who reported 5% maternal mortality in their cohort.[11] There are also some other studies about maternal mortality. Karen Sliwa found that maternal death up to 1 week after delivery occurred in five patients (3.3%) and in another two of 78 patients who presented for follow-up (2.6%) and died within 6 months after delivery. The highest mortality was found in patients with iPAH (3/7, 43%).[4] Miao H reported the overall mortality as 2.8%, decreasing from 6.6% in 2001–2005 to 1.7% in 2016–2020.[12] Regitz-Zagrosek V believes that the mortality remains high in women with PAH (16%–30% maternal mortality).[13]

The outcomes of patients with L-R-PAH were good because in high cardiac output pulmonary hypertension, the decrease in peripheral pulmonary resistance, which occurred during pregnancy, favored a decrease in left to right shunt and PAP. The adverse events in ES-PAH were more severe, and it is advisable that women with ES should be informed of the elevated risk of pregnancy and to avoid pregnancy to prevent adverse outcomes. Our view is consistent with those of Li et al.,[14] Duan et al.,[15] and Kempny et al.[16] Surrogacy as a choice for those with ES was reported to be cost-effective and resulted in significantly improved maternal and neonatal outcomes.[17] The incidence of adverse events in the repaired-PAH group in our study was lower than that of the ES-PAH or sd-PAH groups, similar to the findings of Sliwa et al.[18]

According to the sPAP analysis, a higher level of sPAP corresponded to a higher risk, which was consistent with the findings of Miao et al.[12] Although we found no significant difference in events, such as fetal, neonatal, and child deaths, we attributed this to the limited data analyzed in our study.

ES is associated with significant morbidity and mortality in both mothers and babies. Pregnant women with ES experience hypoxic blood circulation during pregnancy and inadequate placental perfusion, which affects fetal growth and development. Previous studies have suggested that the fetal outcome among mothers with cyanotic heart disease correlated well with maternal hematocrit level. Successful pregnancy is unlikely with a hematocrit level of >65%, and more than 30% of the fetuses have growth retardation.[19] In our study, the outcomes of both the mother and the baby were worse in patients with ES than in those with other PAH subtypes.

Pregnant women with PAH may require general anesthesia.[20,21] Previous studies have reported benefit following treatment with PAH therapies, including oral sildenafil, tadalafil, and prostanoids, during pregnancy. In our study, targeted drugs were used for mothers with severe PAH, and a few patients received anticoagulant therapy. For severe PAH, combined targeted therapy using more than one approach is recommended. Extracorporeal membrane oxygenation was used postoperatively in three cases because of PHC and HF; although all these patients died, extracorporeal membrane oxygenation is a lifesaving measure in cases of severe HF, PHC, and respiratory failure.[13,22,23] Most patients who died had New York Heart Association cardiac function grades of III or IV before pregnancy, which may indicate that pregnancy should have been contraindicated, as recommended by the European Society of Cardiology guidelines.

During the follow-up period, the perinatal period (28 weeks of pregnancy to 1 week after birth) was identified as the period with the highest risk of mortality, PHC, and other risks for mothers. Once the perinatal period passed, PH and cardiac function improved. The outcomes of the L-R-PAH group were good for both the mothers and offspring. In addition, there were four cases (1.8%) where PAH severity improved after childbirth. However, pregnant women with ES and mothers with PAH who continue to suffer from PAH and HF are required to take medication and have limited activity according to the 6-min walking test standard. During the follow-up of the offspring, LBW was noted, together with premature birth, need for additional care, and even death. Fortunately, upon survival, the growth and development of

these infants gradually match those of healthy people in later years.

The multidisciplinary management of pregnant women by experts in the field of pregnant women with PAH-CHD is imperative. In addition to obstetricians and gynecologists, cardiologists, cardiac surgeons, cardiopulmonary bypass specialists, pediatricians, anesthesiologists, surgical intensive care unit specialists, respiratory physicians, and specialists—including clinical geneticists, social workers, and psychologists—should be included in the care of these patients. Appropriate care is necessary, and prepregnancy counseling, along with a detailed clinical assessment of the patient and evaluation of the current hemodynamic situation, including performance of echocardiography and an exercise test, must be provided by experienced cardiologists. The team should monitor all patients with at least moderate-to-severe PAH before pregnancy to provide timely counseling and advice during pregnancy for planning of antenatal care, including delivery and postpartum follow-up, and to ensure that cardiac monitoring can be performed. Some cases of pregnant women with severe PAH in our study were discussed amongst experts from multiple departments or even the whole hospital, resulting in good outcomes for critically ill women. As described in a study by the Pulmonary Vascular Research Institute, further understanding of the effects of sex hormones on the pulmonary vasculature and the right heart and more effective treatment of pulmonary vasculature are promising avenues to explore to improve the outcomes of pregnant women with PAH.[24]

Overall, despite the association of PAH-CHD with increased risk and maternal mortality, most pregnant women included in this study were able to have children. The outcomes for women with L-R-PAH and repaired-PAH were relatively good, whereas those with ES-PAH were serious. In addition to requiring additional monitoring, the offspring of women with PAH-CHD were at a higher risk of premature birth, LBW, and mortality than those of women without PAH. Women with PAH-CHD require prenatal counseling, and a pregnancy team is necessary.[25–27] We agree with Kamp et al.[28] who suggested that an individualized risk-based approach with shared decision-making may be more appropriate to prevent pregnancy in women with PAH than the current guideline recommendations.

This study has some limitations. First, as this was a retrospective single-center study, data were collected from medical records. Thus, some data were incomplete, incorrectly entered, or unavailable, and not enough hemodynamic parameters were provided. Second, we focused on the delivery period, as most patients were referred in the later stages of pregnancy; thus, we were often unable to obtain information on events that occurred earlier in the pregnancy. Third, only a few PAH cases were diagnosed by echocardiography, as echocardiography scans did not evaluate right heart function, for example, TAPSE or the sPAP/TAPSE ratio; thus, we did not have sufficient data to correlate PH severity, other patient characteristics, and treatment with outcomes. Lastly, some follow-up data and the results provided by individual family members may not be accurate owing to privacy concerns.

In conclusion, we revealed that in China, PAH-CHD increases the risks associated with childbirth; however, most patients were able to have children. Thus, mothers with PAH, such as those with ES, should be informed of the increased risk and be advised to avoid pregnancy to prevent adverse outcomes. Pregnant women with severe PAH face problems, such as having to take medications and limit their activities after delivery. Women with severe PAH should be counseled before they conceive, and after they have given birth, they should undergo regular check-ups, such as echocardiograms. Furthermore, careful and close monitoring by an expert team is required, with at least a monthly review. The perinatal period of pregnant women with PAH is associated with problems, such as premature delivery, LBW, and rescue. Although the offspring of PAH women face risks of developmental retardation, growth restriction, and other problems in their early lives, the long-term follow-up results of this study were promising and indicated normal offspring development.

AUTHOR CONTRIBUTIONS

Jiangang Wang: Planning of the study, creation of the study design, revision of the article. **Yang Liu**: Data collection, data summary, data analysis, follow-up, drafting, and revision of the manuscript. **Yanna Li**, **Jun Zhang**, and **Dawei Zhang**: Obstetrics and gynecology data analysis. **Jiachen Li**, **Xiaolong Ma**, **Yichen Zhao**, **Kemin Liu**, and **Chen Bai**: Data statistics, drawing. **Hong Gu** and **Xiangming Fan**: Revision of the article. All authors critically reviewed the manuscript, provided important intellectual input, approved the final version, and agree to be accountable for their contributions.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

All study procedures were conducted in accordance with the ethical standards of the research committee of the Beijing Anzhen Hospital (Approval number: 202151X, Date: November 30, 2021) and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients were informed about the nature of the study and provided oral informed consent. Neither patients nor the public were involved in the design, conduct, reporting, or dissemination plans of our research.

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SUPPORTING INFORMATION

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