

# Pregnancy outcome analysis of 94 patients with pulmonary arterial hypertension during pregnancy

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**Abstract. – OBJECTIVE:** The aim of the study was to analyze the pregnancy outcomes of patients with pulmonary arterial hypertension to provide a reference for clinical diagnosis and treatment.

**PATIENTS AND METHODS:** Clinical data of 94 patients with a pregnancy complicated by pulmonary hypertension were retrospectively analyzed. The means and percentages of the pregnancy outcomes were calculated, and the analysis of variance, Chi-square test, and Fisher's exact test were applied for comparison.

**RESULTS:** The pregnancy outcomes were less favorable in the severe pulmonary arterial hypertension group compared to the mild and moderate groups. The more severe the pulmonary arterial hypertension, the worse the heart function. A poorer heart function was associated with a poorer prognosis across different pregnancy outcomes.

**CONCLUSIONS:** A pregnancy with more severe pulmonary arterial hypertension and worse cardiac function has a poorer maternal and infant prognosis and pregnancy outcome. Cesarean section is the preferred delivery method for patients with severe pulmonary arterial hypertension, whereas vaginal delivery is preferred for patients with mild or moderate pulmonary arterial hypertension and good cardiac function.

*Key Words:*

Pregnancy, Pregnancy outcome, Pulmonary arterial hypertension.

## Introduction

Pulmonary Arterial Hypertension (PAH) is a progressive disease characterized by elevated pulmonary vascular pressure, which can even-

tually lead to right heart failure and even death, whether pulmonary arteriolar vascular disease is present or not. According to previous research, pregnancy, especially during the parturition and postpartum period, is one of the factors that can lead to the progression of PAH, which has a high maternal mortality rate of 9%-30%<sup>1,2</sup>. Although PAH patients are generally advised to prevent pregnancy, as well as termination when pregnancy occurs, an increasing number of women are currently willing to continue their pregnancy, despite the substantial risks for themselves and their unborn child<sup>3,4</sup>. This has led to clinicians paying increased attention to PAH in recent years<sup>5,6</sup>.

The hemodynamic diagnostic criterion for PAH is defined as a mean pulmonary artery pressure (mPAP) measured by right heart catheterization (RHC) of  $\geq 25$  mmHg (1 mmHg = 0.133 kPa) at sea level and in resting state<sup>7</sup>. According to the guidelines for the diagnosis and treatment of pulmonary hypertension in China, its classification includes arterial PAH, PAH caused by left heart disease, PAH caused by respiratory diseases and/or hypoxia, PAH caused by pulmonary artery obstructive disease, and PAH caused by unknown factors<sup>8</sup>. Pregnancy is associated with many physiological changes, affecting hormonal, biochemical, and cardiopulmonary functions. This results in changing hemodynamics and anatomy throughout gestation, during delivery, and postpartum, which can be challenging or even impossible for pregnant PAH patients to adapt to<sup>9</sup>. Additional complications may occur in these patients during pregnancy, leading to an impaired and dangerous clinical course. Therefore, these patients should be rigorously monitored and checked during pregnan-

cy and puerperium<sup>10</sup>. This study retrospectively analyzed the clinical data of 94 pregnant patients with PAH by comparing the effects of different severity levels of PAH on pregnancy, maternal, and infant outcomes. The results can be used as a reference for the diagnosis, treatment, and management of pregnant patients with PAH.

## Patients and Methods

### Patients

To study the pregnancy outcome of PAH patients, we retrospectively analyzed the medical records of 94 pregnant patients with PAH, who were hospitalized in the First Affiliated Hospital of Guangxi Medical University from January 2015 to September 2020. The inclusion criteria were as follows: 1) pregnant patients with a confirmed diagnosis of PAH; 2) patients who either terminated the pregnancy or gave birth in the hospital; and 3) their complete data could be retrieved. Patients who did not fulfill all three inclusion criteria were excluded from the study. Among the 94 included patients there were 46 primiparas and 48 multiparas, with an average age of  $32.71 \pm 5.95$  years and range from 21 to 51 years. The World Health Organization (WHO) has recommended that the frequency of antenatal care should be at least 8 times (during the first 12 weeks of gestation, followed by subsequent contacts at 20-, 26-, 30-, 34-, 36-, 38-, and 40-weeks gestation) to effectively detect, manage, and reduce potential problems<sup>11</sup>. Of the included patients, 63 underwent regular prenatal examination as recommended by the WHO and 31 patients underwent irregular prenatal examination ( $< 8$  times). Furthermore, 17 had a history of cardiac surgery before pregnancy, and 77 patients did not. The etiology of PAH included 47 cases (50.00%) of congenital heart disease, 18 cases (19.15%) of rheumatic heart disease, 7 cases (7.45%) of idiopathic PAH, 7 cases (7.45%) of hypertensive disease during pregnancy, 6 cases (6.38%) of the connective tissue disease systemic lupus erythematosus (SLE), 4 cases (4.26%) of hyperthyroidism heart disease, 3 cases (3.19%) of perinatal cardiomyopathy, 1 case (1.06%) of chronic pulmonary thromboembolism, and 1 case (1.06%) of anemic heart disease. This study was approved by the Ethics Committee of the Guangxi Medical University and conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from the patients and their data were kept confidential.

### Diagnosis and Grouping

PAH was diagnosed as a mean pulmonary arterial pressure of  $\geq 25$  mmHg as measured by RHC at rest<sup>7</sup>. The participants were also evaluated and graded according to the New York Heart Association (NYHA) classification<sup>12</sup>. Two grouping methods were applied in this study to compare the effects of different degrees of PAH and different grades of NYHA classification on maternal and infant prognosis and pregnancy outcome. First, according to the systolic pulmonary artery pressure: results between 25-49 mmHg were classified as the mild group (31 cases); 50-79 mmHg was the moderate group (29 cases), and  $\geq 80$  mmHg (34 cases) was defined as the severe group. Secondly, the participants were also divided into the following two groups according to the NYHA classification: NYHA class I-II group and NYHA class III-IV group.

### Outcomes

The outcomes included patient age, the number of pregnancies and deliveries, causes of pulmonary hypertension, NYHA classification, complications, gestational week and delivery mode, length of intensive care unit (ICU) stay, maternal mortality and neonatal survival rate, neonatal birth weight, and neonatal asphyxia rate.

### Statistical Analysis

Clinical data were recorded and analyzed by SPSS 25.0 software (SPSS IBM, Armonk, NY, USA). The measurement data consistent with normal distribution and homogeneity of variance were presented as mean  $\pm$  standard deviation. Analysis of variance (ANOVA) was used to compare the three groups of data, and a least significant difference test was conducted for pairwise comparison. The counting data were expressed as frequency (rate), for which the Chi-square test was used. When the sample size was  $< 40$  and the theoretical frequency was  $< 5$ , a Fisher's exact test was used. A  $p$ -value of  $< 0.05$  was considered statistically significant.

## Results

### Effects of Different Levels of PAH on Pregnancy Outcome

Thirty-one patients were classified as mild disease, 29 patients as moderate disease, and 34

patients as severe disease according to the cut-off values of systolic pulmonary artery pressure as defined in the methods section. One patient in the severe group refused to terminate the pregnancy at 14 weeks of gestation and died due to aggravation of her condition. There were 23 cases of iatrogenic abortions (24.47%, 23/94), 26 cases of preterm birth (27.66%, 26/94), and 44 cases of full-term birth (46.81%, 44/94). The iatrogenic abortion rate in the severe group was significantly higher than that in the mild and moderate groups, and the full-term birth rate in the severe group was significantly lower than that in the mild and moderate groups. These differences were statistically significant ( $p < 0.05$ ). In the mild and moderate groups, there were 29 cases (93.55%, 29/31) and 22 cases (75.86%, 22/29) of pregnant women with NYHA class I-II, respectively, among which cardiac function grade I-II was the main cardiac function. The proportion of NYHA class III-IV in the severe group was dominant and higher (72.73%, 26/34) than that in the mild and moderate groups, and the differences were statistically significant ( $p < 0.05$ ). The average length of stay in the ICU for 10 pregnant women was  $1.86 \pm 4.26$  days, during which 6 patients (6.38, 6/94) died, and 4 patients (4.25%, 4/94) had a pulmonary hypertension crisis. Pregnant women in the severe group stayed in the ICU significantly longer and the incidence of pulmonary hypertension crisis was significantly higher than that in the mild and moderate groups ( $p < 0.05$ ). A total of 70 neonates were born and survived, which equals a survival rate

of 74.47% (70/94), and their average weight was  $2562.88 \pm 599.98$  g. The neonatal survival rate in the severe group was significantly lower than that in the mild and moderate groups ( $p < 0.05$ ) (Table I).

### Effects of Different Grades of NYHA Classification on Pregnancy Outcomes in PAH Patients

Compared with patients with NYHA class I-II, patients with NYHA class III-IV had lower full-term birth rates (28.57%, 10/35), vaginal delivery rates (2.86%, 1/35), neonatal survival rates (62.86%, 22/35), and higher maternal mortality rates (17.14%, 6/35). These differences were statistically significant ( $p < 0.05$ ). Among the 21 pregnant women with PAH who had a natural birth, 20 with NYHA class I-II were able to endure the delivery, while 1 woman with NYHA class III-IV died after giving natural birth (Table II).

### Gestational Week and Method of Delivery

#### Gestational Week of Delivery

A total of 70 cases were delivered, including 26 cases in the mild group (83.87%, 26/31), 25 cases in the moderate group (86.21%, 25/29), and 19 cases in the severe group (55.88%, 19/34). The delivery rate in the severe group was significantly lower than that in the mild and moderate groups, which was a statistically significant difference

**Table I.** Effect of different PAH levels on pregnancy outcome [N (%) or  $\bar{x} \pm s$ ].

Outcome	Mild group (n = 31)	Moderate group (n = 29)	Severe group (n = 34)
Patients who died before termination of pregnancy	0 (0.00)	0 (0.00)	1 (2.94)
Iatrogenic abortion	5 (16.12)*	4 (13.79)*	14 (41.18)
Premature birth	5 (16.12)	11 (37.93)	10 (29.41)
Full-term birth	21 (67.74)*	14 (48.28)*	9 (26.47)
NYHA class I-II	29 (93.55)*	22 (75.86) *	8 (23.53)
NYHA class III-IV	2 (6.45)*	7 (24.14)*	26 (76.47)
Length of stay in ICU (days)	$0.10 \pm 0.54^*$	$0.28 \pm 0.96^*$	$4.82 \pm 5.99$
Maternal deaths	0 (0.00)*	0 (0.00)*	6 (17.65)
Pulmonary hypertension crisis	0 (0.00)*	0 (0.00)*	4 (11.76)
Cardiac failure	0 (0.00)	1 (3.45)	2 (5.88)
Postpartum hemorrhage	1 (3.23)	1 (3.45)	0 (0.00)
Gestational week of delivery (weeks)	$37.64 \pm 1.53^*$	$36.68 \pm 2.23$	$35.59 \pm 3.10$
Neonatal survival	26 (83.87)*	25 (86.21)*	19 (55.88)
Neonatal weight (g)	$2778.46 \pm 553.58^*$	$2596.00 \pm 540.45^*$	$2224.21 \pm 599.98$
Neonatal asphyxia	0 (0.00)	2 (6.90)	3 (8.82)

Note: \*Statistically significant in comparison with the severe group ( $p < 0.05$ ). NYHA: New York Heart Association.

**Table II.** Effects of different NYHA classification on pregnancy outcomes in PAH patients [N (%)].

Grouping	N	Iatrogenic abortion	Premature birth	Full-term birth	Maternal deaths	Neonatal survival	Cesarean section	Vaginal delivery
NYHA class I-II group	59	11 (18.64)	14 (23.73)	34 (57.63)	0 (0.00)	48 (81.36)	28 (47.46)	20 (33.90)
NYHA class III-IV group	35	12 (34.28)	12 (34.28)	10 (28.57)	6 (17.14)	22 (62.86)	21 (60.00)	1 (2.86)
<i>p</i>	> 0.05	> 0.05	< 0.05	< 0.05	< 0.05	> 0.05	< 0.05	

Note: \*Statistically significant in comparison with the severe group ( $p < 0.05$ ). NYHA: New York Heart Association.

( $p < 0.05$ ). There were 25 cases (80.64%, 25/31), 21 cases (72.41%, 21/29), and 13 cases (38.23%, 13/34) of women with a gestational week of delivery  $\geq 34$  weeks in the mild, moderate, and severe groups, respectively (Figure 1).

**Method of Delivery**

The delivery mode among the 70 cases was cesarean section in 49 cases (70.00%, 49/70) and vaginal delivery in 21 cases (30.00%, 21/70). The rate of cesarean delivery was higher than that of vaginal delivery. The cesarean section rates in the mild, moderate, and severe groups were 53.85%, 68.00%, and 94.74%, respectively. The cesarean section rate of the severe group was significantly higher than that of the mild and moderate groups, and the difference was statistically significant ( $p < 0.05$ ) (Table III).

**Maternal Deaths**

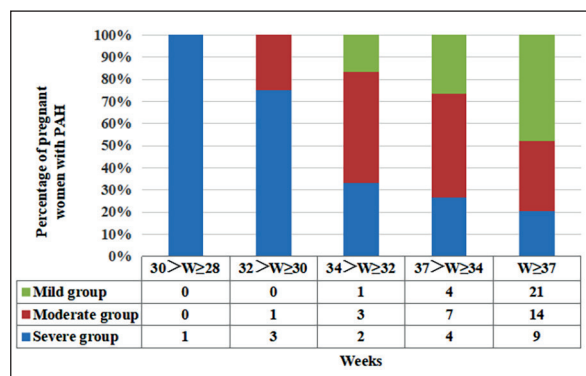
Among the 94 pregnant patients complicated with PAH, 6 patients died, which equals a mortality rate of 6.38%. They were all patients with severe PAH and NYHA class IV. Maternal mortality in the severe group (17.65%, 6/34) was higher than that in the mild and moderate groups, and the difference was statistically sig-

nificant ( $p < 0.05$ ). The death cases are shown in Table IV.

**Discussion**

**Assessment of Cardiac Function and its Impact on Pregnancy Outcomes in PAH Patients**

A previous study<sup>13</sup> in which maternal deaths in the Shanghai Renji Hospital of China were analyzed, showed that pregnancy complicated with heart disease was the first cause of death (37.14%), among which 61.54% of them had moderate or severe PAH, and 23.08% of pregnant women died of pulmonary hypertension crisis caused by severe PAH. It has been well established that cardiac function is an important indicator of pregnancy risk and maternal prognosis. Clinical evaluation of cardiac function in pregnant women is still being conducted according to the heart function classification standard of the NYHA. Both the Chinese medical association and the European society of cardiology (ESC) believe that pregnant women who are complicated with heart disease and belong to NYHA class III-IV are contraindicated for pregnancy, and artificial abortion should be performed as soon as possible once pregnancy occurs<sup>14,15</sup>. In this study, NYHA class I-II was predominant in patients with mild or moderate PAH, and NYHA class III-IV was predominant in patients with severe PAH. A more severe PAH was associated with worsened cardiac function. In PAH patients with NYHA class III-IV, the rate of full-term birth and neonatal survival decreased, and the rate of cesarean section and maternal mortality increased, indicating a poor prognosis of mother and infant. The mortality rate of patients with severe PAH and NYHA class IV was up to 66.67% (6/9). Therefore, attention should be paid to the monitoring of cardiac function in pregnancies complicated with PAH. In contrast, pregnancy should be avoided or



**Figure 1.** Gestational week of delivery.



**Table III.** Method of delivery [n (%)].

Grouping	Number of deliveries (n)	Cesarean section	Vaginal delivery
Mild group	26	14 (53.85)*	12 (46.15)*
Moderate group	25	17 (68.00)*	8 (32.00)*
Severe group	19	18 (94.74)	1 (5.36)

Note: \*Statistically significant in comparison with the severe group ( $p < 0.05$ ).

terminated in time in patients with severe PAH and NYHA class IV.

**Effect of PAH on Pregnancy Outcome**

The third trimester and puerperium are the periods with the highest risk of death in pregnancy complicated with PAH. Ventricular filling and an increased cardiac output can lead to the aggravation of PAH, and complications, such as a pulmonary hypertension crisis, pulmonary embolism, and right heart failure can occur even in patients with NYHA class I-II, leading to maternal death<sup>16</sup>. Although it has been decreasing in recent years, a previous study<sup>17</sup> has reported that the case fatality rate of pregnancy complicated with PAH can be as high as 30%-56%. PAH in pregnancy mainly affects the growth and development of the fetus, which can lead to complications, such as abortion, premature delivery, fetal growth restriction, low birth weight, neonatal asphyxia, and neonatal death<sup>18</sup>. In this study, the maternal mortality rate was 6.38% (6/94), and the maternal mortality rate of patients with severe PAH was

as high as 17.65% (6/34). The leading causes of death were pulmonary hypertension crisis and heart failure. The more severe the degree of PAH, the longer the maternal stay in the ICU, the higher the incidence of pulmonary hypertension crisis and death, the lower the neonatal survival rate and neonatal weight and the poorer the prognosis of mothers and infants, suggesting that PAH severity is closely related to the prognosis of mothers and infants. The results indicated that an increased severity of PAH was associated with longer maternal stay in the ICU, higher incidence of pulmonary hypertension crisis and death, lower neonatal survival rate and neonatal weight, and worse prognosis of mothers and infants. This collectively suggests that PAH severity is closely related to the prognosis of mothers and infants.

**Management of PAH in Pregnancy**

Pregnancy management of PAH patients is closely related to their risk grade of heart disease and pregnancy. The 2018 ESC Guidelines consider the improved WHO risk assessment system

**Table IV.** Maternal deaths.

Case	Age (year)	Etiology	SPAP	NYHA classification	Method of delivery	Gestational week of delivery	Complication	Time of death
1	32	Rheumatic heart disease	85	IV	Cesarean section	29 weeks + 6 days	Cardiac failure	21 days after surgery
2	28	Idiopathic PAH	165	IV	Death before delivery	14 weeks	Cardiac failure	The day of hospitalization
3	24	Congenital heart diseases	125	IV	Abdominal hysterotomy	14 weeks + 4 days	Pulmonary hypertension crisis	On the day of surgery
4	38	Congenital heart disease	93	IV	Cesarean section	37 weeks + 6 days	Respiratory failure	9 days after surgery
5	35	Connective tissue disease (SLE)	85	IV	Vaginal delivery	33weeks+2days	Severe thrombocytopenia	7 days after delivery
6	22	Congenital heart disease	131	IV	Abdominal hysterotomy	27 weeks + 2 days	Pulmonary hypertension crisis	7 days after surgery

Note: NYHA: New York Heart Association.

to be the most accurate assessment system available<sup>14</sup>. However, in China's Expert Consensus on diagnosis and Treatment of Pregnancy complicated with heart disease (2016)<sup>19</sup>, the characteristics of heart disease classification in women of child-bearing age in China have been combined to formulate pregnancy risk assessment and hierarchical management, which can guide clinical work and is more suitable for China's current medical situation and hierarchical referral management. According to the consensus of experts in China, mild PAH is classified as risk of pregnancy grade III, in which the maternal mortality is moderately increased and the maternal and infant complications are strongly increased. Moderate PAH is classified as risk of pregnancy grade IV, which is associated with a significant increase in maternal mortality or stark increase in maternal and infant complications. Furthermore, severe PAH in pregnancy caused by any reason is classified as grade V, which has a very high maternal mortality rate, serious maternal and infant complications, and is a contraindication of pregnancy. The consensus state that grade V pregnancies should be terminated as soon as possible upon diagnosis<sup>15</sup>. In this study, the iatrogenic abortion rate in pregnancies complicated with severe PAH was 41.18% (14/34). However, 25 mild (80.64%, 25/31) and 21 moderate (72.41%, 21/29) PAH patients, had a gestation period of more than 34 weeks. Although mild and moderate PAH are classified as pregnancy risk grade III to IV, most patients can tolerate pregnancy if their heart function is good. Therefore, for patients with mild or moderate PAH who are persistent in continuing the pregnancy, obstetricians, cardiologists, and neonatologists should jointly manage the pregnancy on the premise of fully informing them on the PAH risks. They should comprehensively evaluate whether the patient could continue the pregnancy and when to terminate the pregnancy while taking the patients' wishes, cardiac function, and gestational age into account.

#### ***Gestational Week of Delivery***

For PAH patients who are persistent in continuing the pregnancy, pregnancy should be terminated at any time if the patient can no longer tolerate it, or fetal distress develops. Patients with mild PAH and NYHA class I may give birth at 37 weeks of gestation under close supervision if their condition is stable. Patients with moderate PAH, regardless of NYHA classification, who persist in continuing the pregnancy, should terminate

the pregnancy at 32 to 34 weeks gestation. Severe PAH is a contraindication for pregnancy, and it should be terminated as soon as possible once diagnosed<sup>15</sup>. In this study, of the 70 patients who delivered after 28 weeks, 67.74% (21/26) of patients with mild PAH were able to deliver to term and 84.00% (21/25) of patients with moderate PAH were able to deliver after 34 weeks. As mentioned earlier, pregnancy may be continued under close supervision in patients with mild or moderate PAH if their condition is stable. Most patients with mild PAH do not have evident clinical symptoms, and pregnancy can be closely monitored to term. Patients with moderate PAH have a higher risk of pregnancy complications, and pregnancy termination should be planned after the fetus is mature or viable to avoid disease progression.

#### ***Choice of Delivery Mode***

As for the delivery mode of PAH patients, most scholars believe that cesarean section can shorten the second stage of labor, avoid abdominal pressure, pain, hypoxia, and other stimulation, and reduce the instability of the circulatory system in the delivery process, and is, therefore, the preferred delivery mode for pregnancy patients with PAH<sup>20</sup>. However, the best delivery method for patients with mild or moderate PAH is still controversial. Some scholars believe that vaginal delivery should be the first choice because of the lower risks of postpartum hemorrhage, infection, and thrombosis<sup>21</sup>. In this study, there were 70 cases of live birth, including 49 cases of cesarean section (70.00%) and 21 cases of vaginal delivery (30.00%). The results indicated that higher pulmonary artery pressures were associated with higher cesarean section rates. It is worth noting that 20 of the 21 cases of vaginal delivery involved mild or moderate PAH patients with NYHA class I-II, and all of them could tolerate vaginal delivery. However, one patient with severe PAH and NYHA class IV died during childbirth. Therefore, the delivery method should be considered comprehensively according to the severity of PAH and NYHA classification of patients. Cesarean section is the first choice for terminating a pregnancy in patients with severe PAH, whereas vaginal delivery can be considered for patients with mild or moderate PAH and heart function I-II if delivery can be completed within a short period of time. However, considering the effects of pain stimulation and increased abdominal pressure on hemodynamics during vaginal delivery, it is

suggested to perform labor analgesia to reduce pain and vaginal midwifery technology to shorten the second stage of labor.

There are some limitations in this study, which are mainly related to its retrospective design. Firstly, information bias could be present as the current study included only patients from a single center. However, all pregnant patients with PAH and complete data were included, which makes recall bias or reporting bias unlikely. Another limitation is related to the lack of control in terms of PAH therapy. To further improve the knowledge and management of these highly complex patients, their clinical information, including treatment and long-term follow-up, should be obtained from multicenter records.

### Conclusions

PAH is a serious obstetric complication. The more severe the PAH is, the worse the cardiac function is, and the poorer the maternal and infant prognosis and pregnancy outcomes. Therefore, clinicians need to increase their awareness, identify PAH risk factors early, and perform a rigorous evaluation of pregnancy risk and cardiac function during pregnancy care. For patients with severe PAH and NYHA class III-IV, pregnancy avoidance or early termination is recommended. For PAH patients who refuse to terminate the pregnancy, the appropriate gestational age and delivery mode should be selected according to a comprehensive consideration of PAH severity, NYHA classification, gestational age, and patients' wishes. Cesarean section should be the first choice for patients with severe PAH, and vaginal delivery can be considered in patients with mild to moderate PAH and good cardiac function.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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